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THE CONTRIBUTIONS OF GEORGE RICHARDS MINOT TO EXPERIMENTAL MEDICINE*

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BY ESTABLISHING the George Richards Minot Memorial Lectures, the Section on Experimental Medicine and Therapeutics of the American Medical Association has chosen to commemorate the achievements of a physician whose discovery of a successful treatment for pernicious anemia has resulted in the preservation of thousands of lives. Moreover, Dr. George R. Minot's work stands as a landmark in the notable progress in clinical research of the past thirty years. Indeed, it may properly be described as being a major factor in changing the clinical study of blood dyscrasias from a largely passive and descriptive to an active and critically experimental area of medicine. Not to be forgotten by the medical profession is the fact that this great advance was made by a practitioner of medicine. His subsequent appointment under the full-time academic system as professor of medicine in Harvard University and as director of the Thorndike Memorial Laboratory of the Boston City Hospital fostered the later development of his investigations. Moreover, it allowed him to continue to study various types of blood disorders and nutritional deficiencies under controlled metabolic conditions.

In accepting the responsibility of giving the first of this projected series of lectures in his honor, I can think of no more appropriate topic to discuss than Dr. Minot's remarkable contributions to experimental medicine. Although the successful treatment of pernicious anemia is the achievement for which he will be forever remembered, his interest in medicine contributed fruitfully to other aspects of knowledge of disease. Thus, work by him and his associates has provided important information about the clinical evaluation of the rate of erythropoiesis, the nature of the anemias of scurvy and of iron deficiency, the cause of so-called "alcoholic" polyneuritis, and the pathologic physiology of purpura and of hemophilia and other hemorrhagic diseases, as well as the natural history of polycythemia and the effect of treatment in leukemias. On this occasion, I shall attempt briefly to review some of these contributions and to indicate in retrospect the ideas that, like seeds falling on fertile soil, have made impressive growth.

Dr. Minot, a Bostonian of English ancestry, displayed as an individual the restless activity that perhaps typifies what Emerson called the "mysterious destiny" of the old-time democratic New England community — the ideal of the "conversion of raw material into efficiency." In his approach to scientific and medical problems he often followed and sometimes prescribed for others in effect Hunter's advice to Jenner, "Don't think, try; be patient, be accurate." His achievements were fundamentally due to a persistent curiosity about many things, large or even trivial, in the world around him. He was in essence a biologist whose interests embraced flowers, insects, nutritional disturbances, diseases especially of the blood and every aspect of his patients, including their food and bowel habits, and their emotional and social problems. As a clinical investigator, he possessed an implicit faith in causality that made him optimistic for the future of scientific medicine. The concept of disease as due to deficiency, and therefore as potentially remediable by the addition of something, seemed to fit his instinctive preconceptions. Referring to the importance of close and critical observation, Dr. Minot,[1] the careful but optimistic naturalist at heart, quaintly remarked in an address delivered in Boston in 1929, "One must always be prepared to recognize that but a hair above the underbrush may mean a large mammal is at hand."

That his own capacity for taking infinite pains was the right prescription for his genius is clear from the fact that, although the idea of a relation between good food and good blood was "in the air" and had been brought down to earth by the fundamental work of Whipple and his associates,[2] many physicians fed diets containing liver to patients with pernicious anemia without being convinced or at least without convincing others of their value.

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Only Minot had the instincts and the persistence essential for clear-cut success. Thus, he was prepared to believe that the characteristic remissions of the disease were not "spontaneous." He detected the first slight clinical signs of improvement that followed a change in diet for the better. Together with Dr. W. P. Murphy, he increased the amount of liver to an "optimal" though sometimes nauseating daily amount, and demonstrated over and over again the sequence of liver feeding, beginning clinical improvement, reticulocyte response and subsequent progressive rise of red-cell and hemoglobin levels.

His Nobel Lecture,[3] delivered in 1934, begins with these words: "The idea that something in food might be of advantage to patients with pernicious anemia was in my mind in 1912 when I was a house officer at the Massachusetts General Hospital, as is noted in certain case records there." I can personally testify to the continued interest with which Dr. Minot was accustomed to extract the smallest details of the dietary history from patients with pernicious anemia on the wards of the same hospital in 1922. This was considered by callow interns like myself to be on the whole an amiable eccentricity of an otherwise sound clinician. In this way he established to his personal satisfaction that persons with pernicious anemia often lived on one-sided diets for many years prior to their illness and sometimes developed a disgust for meat at its onset. He believed that the high-fat content of the diet of some of these patients was consistent with the current notion of its hemolytic action, perhaps by promoting intestinal putrefaction. Four years later, in their first published article on the subject "Treatment of Pernicious Anemia by a Special Diet," Minot and Murphy[4] briefly reviewed the record, more than half a century long, of neglected good advice by many physicians regarding the benefits of better diets for the impaired digestion of patients with pernicious anemia. However, it must be confessed that a change of air was often given equal emphasis in the originals of these recommendations. The alleged beneficial use of the forced feeding of meat, as well as the clinical evidence of Gibson and Howard[5] that diets rich in protein and in iron could restore positive nitrogen and iron balances in pernicious anemia, was specifically mentioned. Referred to as the most important and carefully controlled of the existing experimental work tending to support the stated belief of the authors that "adequate proteins as well as iron are necessary for the formation of hemoglobin" was the now classic series of experiments of Whipple and his associates.[2, 6] Their results with both acute and chronically bled dogs had shown the advantageous effects upon hemoglobin production of various foods of animal origin, notably liver.

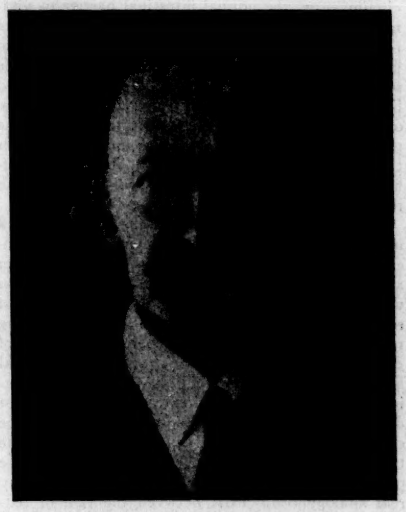
Looking back, one finds it difficult to understand why this great clinical discovery, made in the end by such simple means, was delayed until well into the twentieth century. Probably, this was because, at last, in their own consistently successful dietary regimen, Minot and Murphy[4] knowingly took no chances of inadequacy of dosage or of omitting possible essentials. Apparently in order of importance in their minds was the daily ingestion of 100 to 240 gm. of liver, 120 gm. of "muscle meat," leafy vegetables, especially lettuce and spinach, fruit, eggs and milk. The diet was designed to be "rich in iron and purine derivatives." Fortunately, liver, which must have been chiefly advantageous in the hypochromic anemias of Whipple's dogs because of its iron content, was, as it is now realized, also a good source of vitamin B_{12} and of folic acid. All but 3 of the first 45 patients also received hydrochloric acid, but it was noted that these 3 "improved at least as much as the majority of the others." After admitting that the consistent remissions in their own series of cases "may not last longer than those of others," they conservatively "urged pernicious anemia patients to take a diet of the sort described." This was, of course, the beginning of the end of the reign of terror of the dread disease, and for the time at least it appeared that Dr. Minot would become the patron saint of dietetics.

According to Minot,[3] "it was not until Doctor Murphy's and my observations were well under way that the significance of the reticulocyte reaction as an index of the effect of potent material was fully appreciated." This phenomenon must have been overlooked in the first excitement of discovery, for ten years earlier in an article by Roger I. Lee, Minot and their surgical colleague, Beth Vincent,[7] in a discussion of the significance of reticulated red cells, it is stated that "curves plotted from frequent observations are reliable indicators of bone marrow activity and are the forerunners of increased red cell counts and of clinical improvement. . . ." Again, in 1923, Minot and Sampson[8] refuted spurious claims for germanium dioxide as a remedy for anemia largely on the basis of its inability to cause reticulocyte responses in animal or in man. However, the importance of counting reticulocytes was soon remembered, and at the May, 1927, meeting of the Association of American Physicians, before which body only a year earlier the momentous discovery had been announced, Minot, Murphy, and their associates[9] described the regularity with which a reticulocyte response accompanied the eating of whole liver or the taking of the effective liver fractions first prepared by Professor Edwin J. Cohn. For the testing of the preparations resulting from the latter's "chemical dissections" of liver, the use of the reticulocyte response[10] now became an almost indispensable guide in the never-satisfying rate of progress of the clinical testing of liver fractions. The advantage of this phenomenon was that it

permitted the study of a single patient to yield information about the comparative activity of two or even more preparations.[11] This technic, requiring the daily determination of the reticulocyte percentage during successive and contiguous periods of uniform daily administration of the substance to be tested, became the basis of many of the subsequent early clinical investigations of the pathologic physiology of the nutritional disturbance in macrocytic as well as in hypochromic anemias. It at once supplied the means of readily demonstrating the significant effect upon erythropoiesis in pernicious anemia of normal human gastric juice when brought into contact with beef muscle.[12] Indeed, only since the identification of the active principle of highly purified experimental fractions of liver as the cobalt containing[13] vitamin B_{12}[14] in 1948, and with the even more recent development of suitable microbial and chemical methods for its assay, has it become possible to abandon the tedious estimation of the therapeutic potency of injectable liver preparations by means of the reticulocyte and red-cell responses of patients.

In 1927 the discovery of the basis of the special virtue of liver in pernicious anemia no doubt seemed to Cohn, Minot and their associates[15] likely to be close at hand. Their very first efforts accomplished the immensely important step of a vast reduction in the amount of material required to be ingested by the patient through elimination of the bulky liver proteins. "Fraction G," soon thereafter made available to the medical profession through the collaboration of Eli Lilly and Company with the Committee on Pernicious Anemia of Harvard Medical School, conserved the potency of approximately 240 to 350 gm. of prepared liver in from 9 to 18 gm. of yellow powder. Such daily doses were regularly active in over 160 patients with pernicious anemia.[16] Two other patients with free hydrochloric acid in the gastric contents had responded to liver therapy.[10] This, together with the history of years of defective diet, and the absence of glossitis, icterus and neural manifestations, suggestively identifies them as patients who two decades later would be recognized as lacking in the Wills factor[17] and would be found to respond to folic acid[18] but not to parenterally administered purified liver extracts or to vitamin B_{12}.[19] This first crude liver extract for oral use was also promptly found by others to be effective in the macrocytic anemia of pregnancy, of sprue and of fish tapeworm infestation. In 1931, still others observed that a clarified solution of this extract was thirty to sixty times more effective in pernicious anemia upon parenteral administration than when given by mouth; by 1935, Dakin and West[20] had prepared subfractions with potency comparable to that of the present injectable liver extracts. These, like all types of hematopoietically effective liver extracts, promptly improved the patient with pernicious anemia in all respects (except for the restoration of the gastric secretion), including arrest and often great amelioration of the subacute combined degeneration of the spinal cord.

From the vantage point of present superior knowledge it is interesting to consider what principle or principles in liver caused the regular and complete remissions noted from the beginning by Minot and Murphy. Less is known about liver than about the clinical potency of the so-called Fraction G of Cohn, which was the subject of early and extensive clinical studies by Minot and his associates.[16] When later produced as Liver Extract-Lilly, this yellowish powder in a daily oral administration of 12.75



GEORGE RICHARDS MINOT
1885–1950

gm. usually caused satisfactory reticulocyte and red-cell responses and was accepted as a *U. S. P.* unit (oral). This amount, a daily dose often used, as I have recently learned through the kindness of Mr. G. B. Walden, of Eli Lilly and Company, contains about 25 microgm. of vitamin B_{12} as well as about 100 microgm. each of folic and folinic acids. Now, although the daily oral administration of as little as 5 microgm. of crystalline vitamin B_{12} in some patients has a slight effect upon reticulocytes and very little upon red cells, in most patients even 50 or 100 microgm. daily may do little more.[21] Consequently, it seems probable that the regularity and sustained character of the clinical improvement resulting from the oral administration of Fraction G was the result of the additional presence of folic and folinic acids. Indeed, these are apparently present in

therapeutically effective amounts in this liver extract so that it is active upon oral administration in nutritional macrocytic anemias entirely refractory to purified liver extract (vitamin B_{12}) given by injection.[22] Moreover, recent observations in pernicious anemia[23, 24] clearly demonstrate the increased hematopoietic activity upon oral administration of combinations of small amounts of folic acid and vitamin B_{12}.

The fact that this early orally administered extract was efficient in the arrest of spinal-cord lesions suggests that a certain amount of vitamin B_{12} was absorbed. However, it is now appreciated that the introduction of parenteral liver-extract therapy circumvented the normal intestinal barrier to vitamin B_{12} absorption that is rendered almost absolute by the lack of gastric secretion characteristic of pernicious anemia.[21, 25] Because the early crude solutions of Fraction G as well as the latest refined liver extracts for injection provided about 1 microgm. of vitamin B_{12} per *U. S. P.* unit (injectable), the progressive elimination of folic and folinic acids that occurred in their purification imposed no difficulties in the treatment of pernicious anemia, which requires only injections of pure vitamin B_{12}.

Recent experience supports the validity of a method of testing for the active principle or principles of liver briefly described by Vaughan, Muller and Minot[26] in 1930. A reasonably good correlation was demonstrated between the positive effect of several experimental extracts of liver in causing reticulocyte responses in the peripheral blood of exclusively grain-fed pigeons and their clinical activity. Even earlier, Sabin[27] had found a stimulating effect of crude liver extract on megaloblast division characteristic of blood formation in the chick embryo. However, perhaps because at the time it was difficult to believe that, despite the presence of megaloblasts in the bone marrows, any real analogy could exist between the rate of red-cell formation in apparently healthy pigeons and a deficiency disorder seemingly unique to man, the method was not further explored. Now that recent methods of assaying vitamin B_{12} have utilized chickens fed on proteins solely of vegetable origin, to say nothing of species as remote as Lactobacilli, this earlier work seems plausibly enough to have been on the right track.

In 1930, Mettier, Minot and Townsend[28] reported upon "the effect of food rich in vitamin C on blood formation." Their studies were made upon anemic adult patients with scurvy continued on scorbutic regimens under careful observation on a special metabolic ward. Clear-cut reticulocyte responses and rises of red cells and hemoglobin resulted from the daily oral administration of large amounts of orange juice. Two patients failed to respond to liver extracts devoid of vitamin C, but 1 promptly showed a hematopoietic response to fresh raw-liver pulp. Although these effects were ascribed at the time to vitamin C (not as then isolated), the pure vitamin was subsequently found by others of Dr. Minot's associates not to produce detectable hematopoietic effects in adult scurvy. In the light of present knowledge concerning the requirement of vitamin C for the conversion of folic to folinic acid[29] and the probable relation of this phenomenon to the experimental production of megaloblastic anemia in scorbutic monkeys,[30] it appears likely that the hematopoietic activity of orange juice was due either to the presence of both ascorbic and folic acids or to folinic acid. Interest in this subject has persisted in the Thorndike Laboratory, where Gabuzda has recently shown by microbial analysis that the early hematopoietic results in scurvy were obtained with orange juice probably containing from 300 to 500 mg. of ascorbic, 25 microgm. of folic and 5 microgm. of folinic acid in the dosage employed daily. Moreover, he and his associates[31] have found that the ability of patients with scurvy to excrete folinic acid in the urine is minimal before they are given vitamin C, compared to that capacity in normal persons.

It is recalled at the Massachusetts General Hospital that during the early 1920's one could readily determine when Dr. Minot was on duty as visiting physician to patients on the wards by noting the increased issue of Blaud's pills from the hospital pharmacy. Indeed, as he[32] wrote at about that time, "Iron and arsenic in different forms are the chief drugs that are used in the treatment of anemia." He, as well as others, recognized that iron was "of no value in cases where plentiful amounts of hemoglobin per cell occur, as in pernicious anemia. . . ." Nevertheless, the historical waxing and waning of the popularity of iron in the treatment of anemia was due in part to the clinical fact that in some patients with hypochromic red cells hematologic recovery after blood loss was spontaneous, whereas in others with seemingly similar blood pictures complications such as chronic infections inhibited the therapeutic action of iron. Moreover, the influence of the scientific fallacy of Abderhalden that only organic iron preparations could be converted to hemoglobin persisted long after its abandonment in 1906, and even the multiplicity of dietary factors concerned in Whipple's[2, 6] beautifully controlled studies with regularly bled dogs obscured for a time the evidence that the rate of iron absorption was the chief factor limiting the rate of hemoglobin production in these animals.[33]

To establish the therapeutic significance of iron on a solid foundation, what was chiefly needed, of course, was an objective method of quickly evaluating the response of patients. It was therefore natural, as soon as the reticulocyte response to liver therapy in pernicious anemia had been sufficiently defined, for Minot and his associate Heath[34] to turn their attention to this phenomenon in hypochromic anemia treated with iron. The general validity of

the reticulocyte method was soon demonstrated in this type of anemia also. In many of the elderly female patients with "chronic chlorosis" gastric achlorhydria was present. The well known insolubility of iron salts in neutral or alkaline solutions suggested that iron absorption might be adversely affected by this lack of acid. In observations on such patients, Mettier and Minot[35] employed 200 gm. of beef muscle as a buffer substance to maintain for some time an altered reaction of the gastroduodenal contents. By the use of the ubiquitous reticulocyte response it was shown that erythropoiesis was more active when the same small daily dose of iron was administered with the buffering agent at an acid reaction (pH 3) than at neutrality. In 1932, Dr. Minot's junior associates[36] resolved the confusion resulting from the variable effects upon hemoglobin production of orally administered iron, by demonstrating the existence of a virtually stoichiometric relation between parenterally administered iron and the resulting increment of circulating hemoglobin, at least during the initial stages of blood regeneration. During the recovery of such patients under the spur of iron administration, this priority of demand was later shown by others[37] in the Thorndike group to apply as well to the nitrogen required for hemoglobin building. In these and in other carefully controlled clinical observations many of the fundamental points concerning the absorption and metabolism of iron were established by relatively simple means. They have since been amply confirmed by others using more elaborate though scarcely more convincing methods.

Dr. Minot was fully as interested in other clinical manifestations that he suspected to be the result of faulty diet as he was in the anemias. In 1928 George Shattuck,[38] a colleague in the Department of Tropical Medicine at Harvard Medical School, had suggested that a defective diet might be a factor common both to oriental beriberi and to various forms of "toxic" or "alcoholic" polyneuritis. Strauss, then working in Minot's laboratory, had with McDonald[39] just demonstrated the beneficial effect of improved nutrition in 3 cases of "toxic" neuritis of pregnancy. There was even the interesting historical precedent that, a hundred years before, Dr. Minot's great grandfather, Dr. James Jackson, had written a classic description of alcoholic polyneuritis under the title "On a Peculiar Disease Resulting From the Use of Ardent Spirits." At any rate, in 1933, Minot, Strauss and Cobb[40] reported the results of observations on 57 patients with "alcoholic" polyneuritis, 40 of whom had been treated with a diet rich in complete proteins, minerals and vitamins. The histories of defective diets and of chronic digestive disturbances, together with the apparently beneficial effect of better food, led them to conclude that "dietary deficiency, probably especially of vitamin B_1, plays an important role in the production of 'alcoholic' polyneuritis." A few years later Strauss[41] clinched the evidence in favor of a nutritional deficiency state by showing that improvement of polyneuritis occurred in 10 patients "allowed to continue their customary daily intake of spirituous liquor" in addition to a well balanced, high-vitamin diet supplemented with components of the vitamin B complex.

Dr. Minot made his first contact with the difficult problems of blood coagulation as research fellow in the Physiological Laboratory of Johns Hopkins University School of Medicine. There under the guidance of Professor Howell he spent a year working in active collaboration with another young physician from Boston, George Denny. Together they[42] presented, in 1915, an article clearly demonstrating that circulatory stasis or perfusion of the liver of the dog produced an increase in the antithrombin content of the blood in the hepatic vein. This, together with studies by others of his pupils, led three years later to Howell's successful preparation from liver of the anticoagulant "heparin." The studies of Minot, Denny and Davis[43] on prothrombin and antithrombin factors in the blood of various patients would be differently interpreted today. However, it is of interest that jaundiced patients with bleeding tendencies were observed to have prolonged recalcification times, which the authors attributed to a diminished level of prothrombin. The desire for objectivity of measurement that later served him well is shown by Dr. Minot's short article[44] on the effects of temperature on the coagulation time of recalcified oxalated plasma. These and the subsequent early papers from his pen convey to the reader the sensation of being at the experimenter's elbow. There is a freshness of approach and a wealth of detail that reflect the direct participation of a keen observer at the bedside and at the laboratory bench.

After his return to Boston, he conducted several investigations in association with Roger I. Lee. In 1916 they[45] made a study of platelets derived from the blood of 2 patients with hemophilia. No doubt, owing to technical difficulties in separating these exasperating particles unchanged and completely free of native plasma, they erroneously concluded that the platelets in hemophilia were defective and that this was the essential cause of the slow activation of the patient's prothrombin. However, in this error they were in the good company of Howell and others. Indeed, the matter was not finally settled until thirty years later, when, after the essential plasma defect had been defined by Brinkhous,[46] its embarrassment of the normal activity of hemophilic platelets was demonstrated by Quick.[47] Minot and Lee[45] gave a transfusion of 600 cc. of normal blood to 1 hemophilic patient, with a resulting reduction of the coagulation time from between sixty and one hundred and twenty minutes to seven minutes. A gradual lengthening of the coagulation time then occurred during

the next three days until it reached its original level. The effect of this (at the time) novel procedure was ascribed to the normal platelets so transfused. Twenty years later Patek and Stetson,[48] working at the Thorndike Laboratory, undertook to investigate more extensively this potentially useful phenomenon. Substantial evidence for regarding it as a response to replacement, in the hemophilic patient, of defective prothrombin rather than defective platelets had actually been presented by Addis[49] in 1911. In the course of a series of studies[50, 51] in which Dr. Minot's associates, including F. H. L. Taylor, the biochemist, played a prominent part, a so-called "globulin substance" was prepared from citrated, cell-free normal plasma and found to have the effect of whole normal blood in shortening the coagulation time of hemophilic blood both in vitro and when given intravenously. Globulin fractions of normal plasma devoid of prothrombin and of fibrinogen were equally active. Corresponding fractions of hemophilic blood had little or no effect.

During World War II the development of plasma fractions by Cohn and his associates led to opportunities for testing their antihemophilic activity in Dr. Minot's laboratory. Fraction I was found to carry the antihemophilic-activity globulin, to be suitable for clinical use and to be maximally effective in amounts of 200 to 400 mg. upon intravenous injection into hemophilic patients.[52] Unfortunately, the potential therapeutic value of these advances was found to be limited in practice by the expense of commercial fractionation and by problems that arose in the course of this clinical testing program. Thus, as observed by Frommeyer, Epstein and Taylor,[53] some of the hemophilic patients treated with active fractions eventually developed circulating antibodies demonstrable as precipitins against the active principle of these fractions as well as of whole plasma.

In 1916 extensive study[54] of a young girl who eventually died of idiopathic thrombocytopenic purpura familiarized Dr. Minot with the dramatic manifestations of numerical platelet deficiency. He suspected at that time abnormalities of the plasma of such patients similar to those recently disclosed by Evans et al.[55] and Harrington and his associates.[56] As is usually the case at present, Dr. Minot had no success in agglutinating or in lysing suspensions of normal platelets in dilutions of the serum of his thrombocytopenic patient. Twenty years later, in 1936, he[57] presented a short, clinical description, often referred to, of 3 young adult patients with transient thrombocytopenic purpura associated initially with a marked lymphocytosis. He preferred to regard them as patients displaying purpura hemorrhagica and concomitant lymphocytosis rather than an infection such as infectious mononucleosis accompanied by thrombocytopenia. This was because he had also observed an association between intermittent thrombocytopenic purpura and lymphocytosis sometimes accompanied by eosinophilia recurring with each menstrual period in 3 adult women. In an admirable clinical paper with C. M. Jones,[58] published in 1923, an attempt was made to establish as a clinical entity the cases of infectious jaundice that appeared in the wake of the epidemics of World War I. For the first time attention was drawn to the immature and abnormal lymphocytes and mononuclear cells that appeared during the moderate leukopenia characteristic of the height of the jaundice and the early convalescence of these patients. The authors remarked that these cells resembled those seen in cases of infectious mononucleosis, some of which (without the diagnostic aid of the Paul–Bunnell test) may well have been inadvertently included among their younger patients.

Thrombocytopenia as a result of aplastic or of myelophthisic anemias associated with metastatic cancer of the bone marrow and leukemic infiltration was not always clearly distinguished from idiopathic thrombocytopenic purpura in those far-off days. Consequently, Dr. Minot's papers[59-61] on these subjects added solidity to the meager and scattered information available concerning the various clinical associations and manifestations of decrease in number of these small but important elements of the blood. In 1917 with J. Homer Wright, who in 1910 had demonstrated the origin of the platelets from the megakaryocytes of the bone marrow, Minot studied the plasma factors concerned in the so-called viscous metamorphosis of the platelets. The authors[62] concluded that normally substances in the globulin fraction of plasma concerned in the earliest stages of coagulation and associated with the production of thrombin (but not pure thrombin itself) were the cause of the metamorphosis. This difficult problem has recently been studied again at the Thorndike Laboratory by Jane Desforges,[63] who used the phase microscope for critical inspection of the platelets.

In 1923 Dr. Minot became chief of the Medical Service of the Huntington Memorial Hospital. Here, during the next five years, he was presented with the somber opportunity of becoming acquainted with neoplastic disorders affecting the blood and blood-forming organs. He was impressed with a relation between polycythemia vera and leukemia, and with T. E. Buckman[64] presented a discussion of the pathologic physiology of blood formation and destruction in this disorder. Because the use of short-wave x-ray therapy in the United States had essentially begun only about five years previously and had been made possible at the Huntington Hospital by the installation of suitable equipment, he was able to compare the clinical records of a relatively recent though untreated group of patients with those of a current group treated by irradiation. The three reports of the findings of Minot, Buckman and Isaacs in chronic

myelogenous leukemia,[65] lymphatic leukemia[66] and lymphoblastoma[67] are still standard references. They concluded that — as is true even today with more modern methods of irradiation or the use of chemotherapy in the chronic leukemias — the benefits of treatment were chiefly manifest in a longer-maintained state of good or reasonably good health in relation to the total duration of the disease rather than to an increased duration of life itself. In the management of these chronic conditions, the advantages of the present era not possessed by Minot and his associates consist chiefly in the ready availability of blood for transfusions and of antibacterial chemotherapy.

The literature on blood morphology following irradiation was then in a confused state, and the paper by Minot and Spurling[68] reviewing these articles and reporting on the effects of three different dosage levels of irradiation on a total of 42 patients with localized cancer was in its day a model of carefully planned and executed clinical investigation. The magnitude and duration of the effects observed upon numbers of platelets and upon numbers and types of leukocytes, including the significance of leukocytes as indicators of the amount of irradiation that may safely be applied, have since been amply confirmed by others. At this time also an experimental transfusion of leukocytes was undertaken by Minot and Isaacs[69] in an effort to determine their survival time. Without the use of any anticoagulant, 450 cc. of blood from a patient with lymphatic leukemia and a high leukocyte count was transfused into a patient with advanced lymphosarcoma exhibiting a normal leukocyte count. Most of the transfused cells disappeared within thirty-five minutes, but the pretransfusion level of the recipient's lymphocytes was not reached before two hours and a quarter. As a result of Bierman's[70] recent observations it is now known that even this transient effect would not have occurred if the recipient of the transfused blood had not had leukemia or at least a condition closely related to it. Apparently, in contrast to the patient with leukemia, the lungs of the normal person can remove billions of leukocytes before they pass into the systemic circulation, as Bierman and also Weisberger[71] and their respective associates have convincingly shown.

After his appointment as director of the Thorndike Memorial Laboratory in 1928, Dr. Minot became gradually more deeply involved in the administrative duties of this position and of his appointment as professor of medicine. Of necessity, his part in clinical investigation became ever more that of an intensely interested spectator rather than that of a player in what to him was the greatest of all games. His encouragement from the sidelines stimulated the development of a healthy degree of autonomy for his younger associates who were carrying out investigations in various clinical fields. He maintained a particular interest in the progress of research in blood diseases and in nutritional disorders, and was especially fascinated by the problems of hemostasis. Until his retirement in 1948, he was accustomed to attempt personally to inspire a similar curiosity in each new research fellow who arrived to work with him.

The effect of Dr. Minot's earlier work on the outlook of hematology was immense. Scarcely less important was his later and continuing influence on academic medicine in the United States. This came to pass as a result of the atmosphere of intellectual freedom and the opportunity for hard and productive work that he provided for those fortunate enough to receive appointments in the Thorndike Memorial Laboratory of the Boston City Hospital during the twenty years of his directorship. Today, over forty graduates of that invaluable experience hold professorial titles in various medical schools in this country and abroad.

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A COMPARISON OF THE DIURETIC EFFECTS OF MERCUHYDRIN (MERALLURIDE) ADMINISTERED BY SEVERAL ROUTES*

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THE relative efficacy of the mercurial diuretics by various modes of administration is a matter of considerable practical importance. On intravenous injection, these compounds sometimes produce serious reactions,[1, 2] and because the occasional fatal reaction is confined almost exclusively to this route of administration, there has been a tendency to turn to the intramuscular injection for routine treatment.[3] The desirability of instructing patients in the technic of self-injection to avoid the need of a physician for each dose in the more intensive systems of treatment has focused attention on the subcutaneous injection as a technic that patients or members of the family may master with greater ease.[4, 5] There is lack of agreement concerning relative effectiveness by different routes. Evans and Paxon[6] reported that mercurial diuretics were more effective by the intravenous than by the intramuscular route. Modell, Gold and Clarke[7] found the diuretic responses to Mercuhydrin and Mercupurin by the intramuscular and intravenous routes to be indistinguishable. Batterman, Unterman and DeGraff[8] observed some differences in the response by the various routes of administration.

Observations on this point fail to carry conviction, however, because inadequate methods are used for ascertaining the facts. A method for the bioassay of diuretic agents in ambulant patients with congestive heart failure was recently described in detail by Greiner et al.[9] Briefly, the plan provides for the use of Mercuhydrin by intramuscular injection as the standard against which other drugs or the same drug by different routes of administration is compared. The measure of response is the loss of body weight twenty-four hours after the dose. From dosage-response curves for the standard and the unknown, the effectiveness of the agent being tested is determined. This method of comparison meets the standard requirements for a bioassay. The comparison is so designed as to supply data suitable for statistical analysis, and the precision of the potency of a compound by different routes of administration is expressed in terms of confidence limits. This method has been put to use in the present study.

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EXPERIMENTAL DATA

The organic mercurial diuretic agent used in this study was Mercuhydrin. It was possible to employ this compound by all the routes of administration that we planned to study. For intravenous, intramuscular and subcutaneous injections the sterile multiple-dose vials of 10 cc. of the solution of Mercuhydrin sodium of commerce were selected. For oral administration, we made use of tablets of Mercuhydrin stated to contain 60 mg. of the drug per tablet, and also the tablet of commerce, each stated to contain a similar amount of Mercuhydrin, together with 100 mg. of ascorbic acid. For the rectal route, Mercuhydrin suppositories of three strengths were used, stated to contain 270 mg., 400 mg. and 600 mg. of the drug respectively. (We are indebted to the Lakeside Laboratories, Incorporated, Milwaukee, Wisconsin, for these materials.)

A group of 49 patients participated in these assays, approximately an equal number of adult men and women, the ages ranging from thirty-nine to seventy-nine. All the common etiologic varieties of heart diseases were represented: rheumatic, hypertensive, arteriosclerotic and others. They were ambulant patients in attendance at our cardiac clinics with grades of congestive heart failure varying from moderate to moderately severe. Experience with these patients in various other assays of mercurial diuretic agents had established the fact that twenty-four hours after an effective dose, the average body weight of the group showed a significant fall, returning to the control level by the time the next dose was given. In the plan of these experiments, the patient received the dose at intervals of a week. As seen in the curves discussed below, the response of these patients to the doses in the range employed in these comparisons is a sensitive indicator of differences in doses or efficacy of doses by different routes of administration.

RESULTS

The data are presented in Figures 1 to 3 and Table 1.

Figure 1 shows the comparison of the three routes of injection of Mercuhydrin: intramuscular, intravenous and subcutaneous. Each of the points

represents the same 22 patients. All received each of the three doses by the respective routes. For the kind of statistical analysis of the data applied, the reader is referred to the details of the method described in a previous publication.[9] The statistical calculations fail to reveal a significant difference

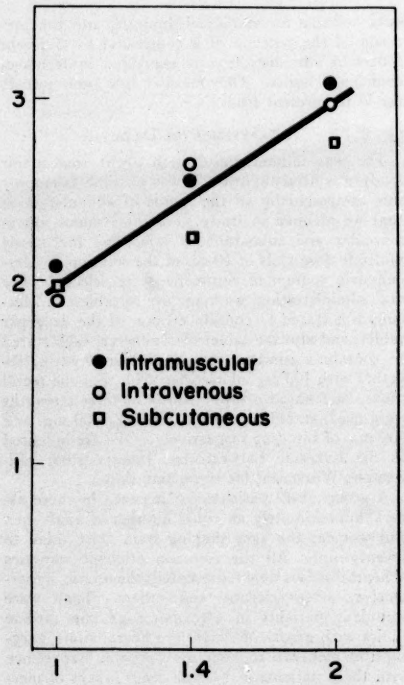

FIGURE 1. *Potency of Mercuhydrin by Three Routes. By intravenous injection, the drug assays 94.6 per cent of the standard (Mercuhydrin by the intramuscular route), with 19 chances out of 20 that the true value lies between 69 and 125 per cent (confidence limits at P = 0.05); by subcutaneous injection, it assays 83.1 per cent (confidence limits of 57 and 108 per cent at P = 0.05).*

in the potency of Mercuhydrin by the three routes of injection.

An attempt to assay the potency of Mercuhydrin in the form of rectal suppositories proved unsatisfactory. In all, 58 suppositories were administered to 21 patients. Despite the use of a Nupercaine jelly for topical anesthesia in the rectum, the suppository was not retained with sufficient regularity, and the fraction of the dose absorbed could not be established with certainty. However, the data obtained suggest that the potency of Mercuhydrin given by rectal suppository under these conditions is about 7 per cent of that given by the intramuscular route. We are at a loss to understand

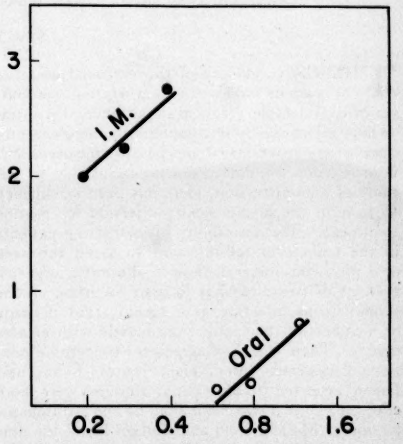

FIGURE 2. *Potency of Mercuhydrin by Oral Administration. Statistical analysis of the data indicates that the chances are 19 out of 20 that the true value for the potency of Mercuhydrin by the oral route is less than 11 per cent of the same material by intramuscular injection.*

the observations of Kissin and Stein,[10] and of Levokove and Sarrow,[11] who reported that the rectal suppository was a satisfactory method for the administration of Mercuhydrin.

Figure 2 shows the potency of Mercuhydrin on

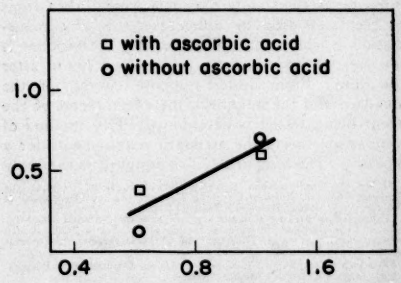

FIGURE 3. *Comparison of the Diuretic Effects of Mercuhydrin by the Oral Route, with and without Ascorbic Acid.*

oral administration in terms of the standard — namely, Mercuhydrin by intramuscular injection. The same 29 patients are represented in both

curves. These curves show that the drug by the oral route has only 4 per cent the potency of this material given by intramuscular injection. Attention may be called to factors that diminished the precision of the oral assay. The precision would be higher if the oral and intramuscular routes were compared in the same range of responses. The local irritant action when the drug was given orally precluded the use of larger doses. In subsequent assays of materials for oral administration, we found it expedient to lower the doses of Mercuhydrin by intramuscular injection to bring the responses by the two routes to approximately the same level. It should also be mentioned that data from experiments in which vomiting or diarrhea complicated the interpretation of the weight loss were excluded from the final calculations. The value for the potency of Mercuhydrin on oral administration stated above is, however, a fair representation of the amount absorbed after an oral dose, in spite of the limitations in the precision of the assay. It compares favorably with the observation of Overman, Gordon and Burch,[12] who found an average of only 5 per cent of the ingested mercury excreted in the urine after the oral administration of Mercuhydrin.

It has been stated in the literature that a mercurial diuretic may produce a more protracted action by the oral route than by injection. We tested this possibility. A group of 13 patients who received oral doses of Mercuhydrin, 480 and 720 mg., were weighed in twenty-four hours and again in forty-eight hours. The average weight loss at the twenty-fourth hour weighing was 0.7 pound, and at the forty-eighth-hour weighing the average weight had increased by 0.2 pound. It is not possible to be certain whether there is any diuretic action after the first day, but it is clear that the major part of the diuretic action of a single oral dose takes place in the first twenty-four hours.

There are reports indicating that ascorbic acid exerts diuretic actions.[13, 14] Shaffer, Chapman and McPeak[15] reported that tablets containing 60 mg. of Mercuhydrin and 100 mg. of ascorbic acid were as effective as 120 mg. of Mercuhydrin alone. We tested this point by an assay, whose results are charted in Figure 3. The same 20 patients are represented in the data pertaining to Mercuhydrin alone and in those of Mercuhydrin with ascorbic acid. Our results fail to confirm the report that ascorbic acid in the doses used enhances significantly the diuretic action of Mercuhydrin on oral administration.

Table 1 presents the results pertaining to gastrointestinal irritation from the oral administration of Mercuhydrin with and without ascorbic acid. It may be seen that in approximately a third of the patients unpleasant gastrointestinal symptoms followed a single dose of twelve tablets (720 mg.), a dose that produced a small diuretic effect. The number of patients in whom such symptoms occurred fell to 11 per cent when only six tablets were given, but the diuretic effect of this dose was negligible. It may also be seen that ascorbic acid did not influence the local irritant action of the organic mercurial.

On the supposition that the local action of a high concentration of the drug in the form of a tablet might be responsible for the gastrointestinal irritation, we gave by mouth the solution of Mercuhydrin sodium that is commonly used for injection. The doses were 3, 4.2, and 6 cc., respectively, representing the Mercuhydrin content of six, eight and twelve tablets. A preliminary trial of 16 doses in 10 patients produced nausea in 12 per cent, vomiting in 12 per cent, abdominal cramps in 12 per cent and diarrhea in 31 per cent. The use of Mercuhydrin sodium in the form of a solution did not reduce the frequency of gastrointestinal irritation.

TABLE 1. *Gastrointestinal Symptoms with Mercuhydrin Given by Mouth.*

DOSAGE	AS SOLUTION DOSE IS EQUIVALENT TO	TOTAL PATIENTS	INCIDENCE (PATIENTS) OF GASTROINTESTINAL SYMPTOMS§	NO. OF DOSES GIVEN	TYPES OF TOXICITY				INCIDENCE (DOSES) OF TOXICITY
					CASES OF NAUSEA	CASES OF ABDOMINAL CRAMPS	CASES OF VOMITING	CASES OF DIARRHEA	
mg.	*cc.*		%						%
Mercuhydrin alone:									
360*	3	35	11	39	3	—	1	1	13
480*	4.2	31	18	32	1	4	—	1	19
720*	6	32	31	41	1	4	3	8	39
Mercuhydrin with Ascorbic acid:									
360*†	3	27	13	30	—	1	2	1	13
720*‡	6	25	32	26	2	1	1	5	25

*These doses were given in the form of tablets.
†60 mg. of ascorbic acid.
‡120 mg. of ascorbic acid.
§When a patient received a particular dose twice but experienced gastrointestinal symptoms after only one, the incidence was counted as ½.

Summary and Conclusions

A method for the bioassay of diuretic agents in ambulant patients with congestive failure, which meets the standard requirements of a scientific assay, was employed for the comparison of the diuretic efficacy of Mercuhydrin by various routes of administration.

The results show that a dose of Mercuhydrin produces substantially the same amount of diuretic effect, when given by intravenous, intramuscular or subcutaneous injection.

Mercuhydrin is much less effective by the oral route than by injection; it takes approximately twenty-five times as much by oral administration as by intramuscular injection to produce the same effect, and the largest doses given by mouth in this study, which caused gastrointestinal irritation in approximately a third of the patients, produced only a small diuretic effect, equal to that of less than 0.5 cc. of Mercuhydrin by intramuscular injection.

The results of this study fail to confirm the belief that ascorbic acid in the doses commonly used enhances the diuretic action of Mercuhydrin or that ascorbic acid reduces gastrointestinal irritation after oral doses of the mercurial.

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SUCCINYLCHOLINE: A NEW APPROACH TO MUSCULAR RELAXATION IN ANESTHESIOLOGY*

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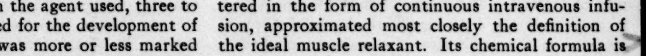
IT IS generally accepted that the ideal muscle relaxant should have specificity and rapid onset of action, readily controllable intensity, wide margin between muscular relaxation and respiratory arrest and rapid and complete recovery after the cessation of its administration. The agents hitherto employed for the production of muscular relaxation in surgical anesthesia all fell short of the above requirements. Depending on the agent used, three to eight minutes were required for the development of maximal effect.[1-3] There was more or less marked respiratory depression with all agents, and in a certain percentage of patients adequate muscular relaxation could not be obtained without transient respiratory arrest.[1-3] Salivation, excessive bronchial secretion, bronchospasm, tachycardia, hypotension and hypertension were encountered in various combinations with the different muscle relaxants.[1-6] The duration of action of a single effective intravenous dose varied from ten to thirty minutes with these agents; an even longer time was occasionally required for the complete restitution of neuromuscular conduction after prolonged administration of fractional doses. Occasionally, profound respiratory depression of long duration could be observed.[1-3, 7]

Observations made on anesthetized patients with a recently introduced synthetic muscle relaxant, succinylcholine, indicated that this agent, administered in the form of continuous intravenous infusion, approximated most closely the definition of the ideal muscle relaxant. Its chemical formula is



Succinylcholine was synthesized by Hunt in 1906.[8] Its neuromuscular blocking activity was first observed in 1949 by Bovet,[9] and reported simultaneously and independently by Phillips.[10] Subsequently, it was investigated by Castillo and de Beer[11] and de Beer et al.[12] in various laboratory animals. Succinylcholine belongs to the "depolarizing" type of neuromuscular blocking agents.[13] Its effect is intense, brief and reproducible. The short duration of the action of a single intravenous dose

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was attributed to the rapid enzymatic hydrolysis of succinylcholine.[10-12, 14-16] The duration of action can be prolonged by physostigmine.[12]

Clinical trials with succinylcholine were reported by Brücke et al.,[17] Thesleff[18] and Dardel and Thesleff,[19] and with a closely related compound, di-(B-ethyl-dimethylammonium-ethyl) succinate diiodide by Voldoni[20] and Ottolenghi[20] and also by Scurr.[21]

Material and Methods

The observations presented below were made on 202 unselected consecutive patients in whom the use of muscle relaxant was indicated. Of these, 79 were males and 123 were females. The age distribution is presented in Table 1.

Table 1. *Age Distribution of Patients.*

Age Group	No. of Patients	Percentage
yr.		
11–20	5	2.5
21–30	17	8.4
31–40	35	17.3
41–50	57	28.3
51–60	48	23.8
61–70	26	12.8
71–80	10	4.9
81–90	4	2.0
Total	202	

Anesthetic Technic

After premedication with pentobarbital, atropine or scopolamine and morphine, patients were anesthetized by the intravenous injection of a 2.5 per cent Pentothal Sodium solution administered through the rubber sleeve of an intravenous infusion of 5 per cent dextrose started previously. After the depth of anesthesia progressed to Plane 1 or 2 of Stage III, 10 to 45 mg. of succinylcholine di-iodide* was administered intravenously. Forty-five to sixty seconds later the vocal cords were visualized by direct laryngoscopy and sprayed with a 1 per cent Pontocaine solution, and an endotracheal tube was inserted. The intubation was usually completed within one or two minutes from the end of the administration of succinylcholine. A continuous intravenous drip of an 0.2 per cent solution of succinylcholine di-iodide in physiologic saline solution or in 5 per cent dextrose in water was started immediately after intubation through a No. 23 needle also inserted into the rubber sleeve of the intravenous infusion started before the induction of anesthesia. One obtained the degree of muscular relaxation required by regulating the rate of flow of the succinylcholine solution with a "tunnel clamp."† From then on the anesthesia was conducted as described previously.[1-3]

*Kindly supplied by Dr. E. J. de Beer, of Burroughs, Wellcome and Company, Incorporated, Tuckahoe, New York.

†Obtainable from the Harvard Instrument Company, Dover, Massachusetts.

Succinylcholine was used for the production of muscular relaxation in various types of cases (Table 2).

Results

The rapid intravenous injection of 10 to 45 mg. of succinylcholine di-iodide was occasionally followed in thirty to forty-five seconds by muscular twitchings of five to fifteen seconds' duration. At the same time the respiratory depth also increased. Muscular relaxation developed in forty-five to sixty seconds, reaching its maximum in sixty to ninety seconds. After one hundred and eighty seconds, the effect of a single injection of succinylcholine started to decrease, and disappeared within three hundred seconds.

Table 2. *Types of Operations.*

Operation	No. of Cases	Percentage
Gastric	43	21.3
Gall bladder	57	28.2
Other upper abdomen	38	18.8
Large bowel	20	9.9
Appendectomy	8	4.0
Intra-abdominal gynecologic procedure	36	17.8
Total	202	

Muscular relaxation could be maintained by the continuous intravenous infusion of 1.1 to 9.2 mg. of succinylcholine di-iodide per minute. The average dose of succinylcholine di-iodide was 4.0 mg. per minute. The degree of relaxation could be changed within thirty seconds by regulation of the flow rate. It was our clinical impression that good muscular relaxation could be obtained with less respiratory depression than with any of the other muscle relaxants. Assisted respiration was seldom necessary, and respiratory arrest never developed, except when produced deliberately with excessive flow rates. The effect of succinylcholine on muscular relaxation and respiratory depth completely disappeared in all cases within two to four minutes after the intravenous infusion was discontinued.

Table 3. *Succinylcholine Di-iodide and Pentothal Sodium Requirements.*

Requirement	Range	Average
Duration of anesthesia	35–363 min.	126 min.
Initial dose of succinylcholine di-iodide	10–50 mg.	29.2 mg.
Total dose of succinylcholine di-iodide	66–1830 mg.	597 mg.
Dose of succinylcholine di-iodide per minute	1.1–9.2 mg.	4.0 mg.
Initial dose of Pentothal Sodium	250–1000 mg.	560 mg.
Total dose of Pentothal Sodium	540–3500 mg.	1432 mg.
Dose of Pentothal Sodium per minute	2.3–34.8 mg.	13.1 mg.

The quantities of succinylcholine and Pentothal Sodium used are summarized in Table 3.

The quantity of Pentothal Sodium per minute necessary for the maintenance of an adequate depth of anesthesia, characterized by the absence of breath holding, was found to be the same as that

of Syncurine[1] but somewhat greater than that of Mytolon Chloride[2] or Flaxedil.[3] The significance of this finding is discussed below. Despite this, 50 per cent of the patients reacted to stimuli after the removal of the endotracheal tube. The average recovery time in the rest of the patients was considerably longer (seventy-nine minutes) than after the use of other relaxants.[1-3] In contrast to this, respiratory depression, seen in 12 to 21 per cent of the patients after the use of other muscle relaxants,[1-3] was not observed in any of the patients after the use of succinylcholine.

Postoperatively, atelectasis was observed in 2, and moderately increased bronchial secretions were found in 29 of the 202 patients who received succinylcholine for prolonged periods. The only other serious respiratory complication was bronchopneumonia in a debilitated patient with peritoneal carcinomatosis. This patient came to the operating room with a temperature of 103.4°F. Through a small laparotomy incision 8000 cc. of fluid was removed. Bronchopneumonia, diagnosed a few hours postoperatively, responded promptly to intramuscular injection of penicillin.

The incidence and severity of other postoperative complications did not differ significantly from those observed after the use of other muscle relaxants. There were 10 postoperative deaths in this series. The deaths occurred two to forty-nine days postoperatively. In no case was there any connection between the patient's death and the use of succinylcholine.

TABLE 4. *Circulatory Changes.*

OBSERVATION	PULSE RATE		SYSTOLIC BLOOD PRESSURE		DIASTOLIC BLOOD PRESSURE	
	RANGE	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE
Initial value	58–136	85	80–300	122	40–142	75
Value ten minutes after start of anesthesia	48–180	89	74–228	120	38–142	76
Lowest value observed during anesthesia	48–120	81	68–222	106	34–122	69
Highest value observed during anesthesia	70–130	100	84–270	139	50–140	87
Value at termination of anesthesia	60–140	93	85–260	123	40–122	75

DISCUSSION

Compared to other muscle relaxants used in anesthesiology, succinylcholine possesses several advantages, the outstanding one, in our experience, being its easy controllability, which permitted almost instantaneous changes in the degree of muscular relaxation. No other agent used in anesthesiology can be as readily controlled as succinylcholine. Although it is possible to increase rapidly the depth of anesthesia after intravenous administration of barbiturates, recovery is never prompt. Even with the most rapidly acting inhalation agents, such as cyclopropane and ethylene, it takes minutes to deepen or lighten the depth of anesthesia. With succinylcholine, both the increasing and the decreasing of muscular relaxation took less than a minute.

The reason for this ideal controllability is the fact that succinylcholine, in contrast to the other generally employed muscle relaxants, is rapidly hydrolyzed by both cholinesterase (plasma cholinesterase, nonspecific cholinesterase) and acetylcholine esterase (true cholinesterase).[15] It has been shown that the hydrolysis of procaine and 2-chloroprocaine by the plasma cholinesterase[22] is a zero-order reaction.[23] It seems permissible to assume that succinylcholine is hydrolyzed in an identical manner. This would mean that above a certain critical concentration the quantity of succinylcholine hydrolyzed per minute in the body would be independent of its concentration. Consequently, a more rapid continuous administration of succinylcholine will cause an elevation of its concentration and produce a more profound muscular relaxation. On the other hand, the enzymatic hydrolysis of succinylcholine di-iodide is so rapid in vivo that, in the average patient, the effect of a 30-mg. dose, which produces complete muscular relaxation, completely disappears within five minutes. This rapid, and to all appearances complete, hydrolysis of succinylcholine explains the lack of residual respiratory depression frequently seen with other muscle relaxants that are not similarly disposed of within the organism. The residual respiratory depression with other muscle relaxants that can be profound and prolonged in the occasional patient presented a serious enough problem to necessitate the use of various "anticurare" drugs.[24, 25] These drugs — physostigmine, prostigmine, Tensilon and so forth — are only effective against the "antidepolarizing" group of muscle relaxants (d-Tubocurarine, Metubine and Flaxedil), and their use can also be accompanied by various undesirable side effects[26] and even death.[27, 28] Recently, a compound was synthetized that is capable of antagonizing the effect of Syncurine on neuromuscular conduction.[12] The dangers that might be encountered with the use of these drugs have been discussed elsewhere.[29] Because of its rapid and complete hydrolysis, these problems are nonexistent with the use of succinylcholine.

It was observed that the rapid intravenous injection of 100 mg. of procaine in patients receiving a muscle-relaxing dose of succinylcholine increased the degree of muscle relaxation and produced respiratory depression. Since procaine is also hydrolyzed in the organism by the nonspecific choline esterase,[22] the additive effect of procaine adminis-

tration on succinylcholine activity can be looked upon as substrate competition for the same enzyme. Further observations on this phenomenon will be presented elsewhere.[30]

Another advantage of succinylcholine is its relative sparing effect on respiration. With comparable muscular relaxation, there is definitely less diminution of respiratory depth, and the respiratory movements are smooth, in contrast to the jerky respiration frequently seen with other muscle relaxants. We have no explanation of this favorable circumstance. It is possible that the depressant effect of succinylcholine on the central nervous system is less marked than that noted with other muscle relaxants.[31] Ellis et al.[32] found that the depressant effect of succinylcholine on the respiratory center was less than that of Syncurine or d-Tubocurarine. The lack of unwanted side effects with the use of succinylcholine was very gratifying. No marked circulatory changes were seen (Table 4). The slight variations in pulse rate and blood pressure seemed to be dependent on surgical manipulation. If anything, there was a tendency for a slight elevation of pulse rate and systolic blood pressure. Salivation, excessive bronchial secretions, laryngeal spasm, bronchospasm and other evidences of histamine release were not observed. There was no indication of blocking or stimulating action on the autonomic nervous system.

The disadvantages of succinylcholine are not serious. The first of these is that its administration requires greater attention on the part of the anesthesiologist. One must regulate the rate of its administration by adjustment of the drops delivered per minute, and the rate of flow has to be checked periodically and adjusted to the degree of relaxation required by the surgeon. The use of a tunnel clamp and stop watch or Flowrator[33] facilitates the rapid regulation of the flow.

The second disadvantage of succinylcholine in our experience was that somewhat higher doses of Pentothal Sodium per minute were required for the maintenance of comparable depth of anesthesia than with the other synthetic muscle relaxants.[29] Consequently, though the percentage of patients who reacted to light stimulation at the end of anesthesia compared favorably with that seen with other muscle relaxants, the average recovery time of the remainder of the patients was considerably longer (seventy-nine minutes as compared to thirty-three to forty-eight minutes).

That the per minute dose of Pentothal Sodium was greater with succinylcholine than with the other muscle relaxants studied previously might be due to the fact that the succinylcholine molecule has less depressant action on the central nervous system.[22]

The available data on the effects of succinate on barbiturate anesthesia are controversial.[34] It was suggested by Soskin and Taubenhaus[35] that succinate might be a physiologic antidote in barbiturate anesthesia. Recently, Price[36] demonstrated that the intracarotid injection of sodium succinate increased the electrical activity of the brain in rabbits. On the other hand, Corson et al.[37] found that the recovery time in barbiturate anesthesia was not significantly shortened by succinic acid. The investigations of Tucci and his coworkers[38] and Vandewater and Gordon[39] also gave negative results. Lamson and his associates[40] found that succinates prolonged the duration of sleep in guinea pigs after the administration of barbiturates. On the basis of presently available evidence, it seems more likely that the less marked central depressant effect of the succinylcholine molecule, and not the antagonistic effect of the succinate molecule, is responsible for the somewhat increased Pentothal Sodium requirements.

The occasional muscle twitching that can be seen on rapid administration of succinylcholine also occurs, though less frequently, with the use of Syncurine.[13] This transient muscular twitching is due to the initial stimulating effect of these depolarizing compounds on skeletal muscle. A slower rate of intravenous injection of Syncurine and succinylcholine will usually prevent these fasciculatory movements.

The advantages of succinylcholine as a muscular relaxant in anesthesiology far outweighed its disadvantages. The greater attention required on the part of the anesthesiologist was amply rewarded by the greater flexibility afforded by this agent. Similarly, the complete absence of residual respiratory depression and the lack of side effects more than compensated for the occasionally observed prolonged sleeping time, which was due to the increased quantity of Pentothal Sodium used.

On the basis of our experience, succinylcholine is the muscle relaxant of choice, especially in debilitated, dehydrated and aged patients, in whom prolonged postoperative respiratory depression with other agents is most common.[29]

It is highly significant, from both the pharmacologic and clinical points of view, that succinylcholine exerts its desired effect rapidly, is readily controllable and is easily hydrolyzed into substances that in the dose range employed have no harmful effects. The need for such ultrashort-acting agents in anesthesiology is readily apparent, and it is hoped that the clinical use of succinylcholine will stimulate the search for other agents — for example, barbiturates — with ultrashort activity.

Summary

Succinylcholine is an ultrashort-acting, "depolarizing" type of muscle relaxant with a rapid onset and short duration of action. This short duration of action is due to the rapid enzymatic hydrolysis of succinylcholine within the organism.

For prolonged muscular relaxation it has to be administered in continuous intravenous infusion. The degree of muscular relaxation can easily be controlled.

It has a relative sparing effect on respiration during its administration, and because of its rapid hydrolysis its use is not followed by respiratory depression.

Its use is not accompanied by unwanted side effects, and the incidence of postoperative complications is low.

On the basis of limited experience, succinylcholine seems to be the muscle relaxant of choice of all similar agents so far investigated.

Addendum

Since this paper was submitted for publication several cases of prolonged respiratory depression after the use of succinylcholine have been reported.[41-44] As pointed out elsewhere[45-47] unnecessarily high doses of succinylcholine were used in these cases. It has also been shown that the depressant effect of a given dose of succinylcholine on respiration is inversely proportional to the plasma cholinesterase activity of the patients.[48, 49] According to our experience in over 500 cases in which succinylcholine was administered in the manner described in this paper, no prolonged respiratory depression was observed. Low plasma cholinesterase activity could be detected from the effects of the initial dose of succinylcholine, and if the maintenance dose was adjusted to the needs of the patients the restitution of respiration after the discontinuation of the succinylcholine administration was not markedly different from that in patients with normal plasma cholinesterase activity. On the other hand, if patients with low plasma cholinesterase activity receive unnecessarily high doses of succinylcholine, the development of prolonged respiratory depression cannot be avoided.

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THE GENERAL PRACTITIONER AND CANCER OF THE EAR, NOSE AND THROAT*

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THERE are few orifices of the body through which symptoms of disease can be detected with such ease as the ears, nose and throat.[1]

It is true that cancer in this region of the body is not so common that it is seen every week, or even every month, in the general physician's office but a few figures demonstrate how common it can be. Despite the fact that the Ear, Nose and Throat Tumor Clinic at the Massachusetts General Hospital meets one morning a week, records show 1750 visits to this clinic during the past year as compared with the 10,434 over-all visits to the entire Tumor Clinic for the same period. At Pondville Hospital, which serves a rural area, the Ear, Nose and Throat Tumor Clinic has had 348 such visits within the past year in its clinics held one morning a week. These are exclusive of the house patients, who are admitted directly to the hospital. This figure compares with the over-all 10,200 cases seen in that entire Tumor Clinic in the past year.

Leach and Robbins[2] reported that there has been no significant improvement during the last decade in the ability of doctors to recognize symptoms suggestive of early cancer in spite of the fact that patients are definitely reporting their symptoms earlier in the disease.

Cancer prognosis is all too often regarded in terms of high mortality even with early diagnosis. This type of pessimism is unwarranted. Of all the cases of cancer of the paranasal sinuses seen at the Massachusetts Eye and Ear Infirmary[3] over a fifteen-year period, regardless of the stage of the disease, 27.5 per cent are reported as five-year cures. Such a figure is distinctly encouraging, because many late cases are included; also, the series included many patients who were first treated when knowledge of the best type of therapy was less extensive than at present.

So far as laryngeal cancer is concerned, early cases should have an 85 to 92 per cent five-year-cure rate. Even the more extensive lesions of the larynx have a 55 to 65 per cent chance for a five-year cure because of the advances in x-ray therapy as well as the possibilities offered by total laryngectomy, with or without radical neck dissection. No other area of the body except the skin gives a better chance for cancer cure than the ear, nose and throat.

In this field optimism in the approach to cancer is warranted; the physician can give his patient the optimum chance for cure if the diagnosis is made early. In this respect the general practitioner becomes his own cancer-screening clinic.

What makes one suspicious of cancer of the nose or sinuses? Epistaxis, particularly in adults, should be carefully evaluated. If no bleeding point is noted anteriorly in the common area of the septum, the nasal passages should be studied back to and including the postnasal space. Persistent unilateral bloody discharge in adult patients is a sign of cancer of the nose or sinuses unless proved otherwise. Persistent pain in the upper teeth in the absence of acute infection may suggest neoplasm in the antrum. Patients frequently consult their dentists, and the teeth may be stated to be sound. X-ray examinations of the sinuses are essential for revealing disease in the antrum itself. Painless swelling of the cheek is a common complaint and finding. In edentulous people the first complaint to suggest cancer of the maxillary sinus may be, "My upper denture doesn't fit any more." The expansion of a tumor involving the floor of the antrum may produce that single early sign. Paresthesias of the cheek and even slight unilateral exophthalmos are highly suggestive of neoplasm of the antrum.

In every suspicious case x-ray studies, repeated if necessary at intervals of a few weeks, are indicated. If the symptoms are sufficiently suspicious, exploration of the antrum is indicated. In this series, best results were shown in patients with antral cancer who had surgical treatment primarily, with supplementary radiation in chosen cases.

Examination of the nasopharynx is most often neglected mainly because skilled use of the head mirror and indirect mirror have never been developed by enough general practitioners. It is true that one cannot be proficient in all the arts and tools of the specialist, but this ability should be developed by anyone who examines the orifices of the head.

In nasopharyngeal cancer one may not be aware of the lesion until cervical adenopathy appears; by that time, in most cases, cures are rarely possible. However, many symptoms suggest early diagnosis of cancer in this region, particularly when two or three appear in close order. Nasal obstruction, postnasal bleeding, epistaxis, tinnitus and hearing loss are the more common complaints and, when they appear simultaneously, should suggest cancer of the postnasal space. When this diagnosis is suspected, x-ray study of the nasopharynx and base of the skull is indicated and may give information about abnormal swelling in the nasopharynx. The usual picture by mirror or nasopharyngoscope in the nasopharynx is that of an irregular, rough, granular outcropping with or without ulceration, usually unilateral when early. As a result of a recently reported series[4] a 27 per cent chance for a five-year cure can be predicted in early cases,

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whereas, as recently as 1940, only the very rare case was reported cured. This represents progress.

The treatment of cancer of the nasopharynx is almost entirely in the hands of the radiologist. Results would be much better if more of these so-called primary lesions could be diagnosed and treated before they metastasized to the neck.

New growths of the tonsil are insidious in onset and may produce very few symptoms. The dentist and general practitioner have the best opportunity for early diagnosis of cancer of this organ. Any unilateral enlargement of a tonsil, with or without ulceration, should arouse suspicion. Any ulceration of a tonsil that does not show signs of clearing up with treatment within a week or so should suggest cancer, and biopsy would be indicated. Dysphagia and a feeling of a persistent lump in the throat may not appear before the tumor involves the palate, when bloody expectoration and otalgia may also ensue. The diagnosis must be made early because once the tumor invades the palate or metastasizes to the glands at the angle of the mandible, the prognostic curve drops precipitously. X-ray therapy is the treatment of choice for tonsil cancer. At present the rate of five-year cures in skilled radiotherapy of primary carcinoma of the tonsil ranges from 20 to 30 per cent. Lampe,[5] a skilled therapist, has made the statement that "to elevate the cure rates no new methods of treatment are required, only better management is needed."

Again, the head mirror and laryngeal indirect mirror come into use in the follow-up study of suggestive symptoms relating to the hypopharynx or larynx. Persistent pain in the throat on swallowing and lumpy sensations in the throat on swallowing of liquids and solids are suggestive of cancer of the hypopharynx. As a differential point, in ordinary pharyngitis the patient complains of a lumpy sensation on swallowing liquids, but this sensation usually disappears when solids are swallowed because the bolus of food keeps the opposing surfaces of the inflamed mucosa from touching. Only when a tumor of the hypopharynx is so large that it obstructs the entrance into the larynx does dyspnea occur. Hemoptysis and cough associated with odynophagia are not uncommon with tumors of the hypopharynx. Mirror examination reveals an irregular, rough, usually ulcerated outcropping of the epiglottis or pyriform fossae. If the laryngeal mirror cannot be used barium-swallow and x-ray examination of the hypopharynx is indicated and can be helpful in diagnosis.

In intrinsic cancer of the larynx hoarseness occurs relatively early. Persistent hoarseness of more than three weeks' duration not only deserves but also demands a laryngeal examination. Gargles and tonsillectomies do not cure such hoarseness. Cough, hemoptysis, pain in the region of the larynx and dysphagia occur later on as the cancer enlarges and encroaches on the full body of the larynx itself.

The best therapeutic results are obtained in cases of cancer of the larynx, and this is one area in which diagnosis is possible in almost all cases. If the general practitioner is not skilled in the use of the laryngeal mirror, patients with persistent hoarseness of more than three weeks' duration should be referred to someone trained to do such an examination. In the typical lesion mirror examination will show an irregular outcropping or ulceration of a cord. Cancer of the larynx[6] has been discovered in all decades of life, and age should be no deterrent to careful evaluation of the cause for the hoarseness. Both surgery and x-ray therapy have a specific place in the treatment of cancer of the larynx, with gratifying results in properly chosen cases.

Recent studies by the National Cancer Institute[7] show a 75 per cent increase in the incidence of laryngeal cancer and a 42 per cent increase in mortality in comparing the statistics of the year 1937 with those of 1947 in five major American cities. This mortality rate can be decreased with present knowledge of this disease.

Cancer of the ear is less common, but here again early diagnosis is essential. Any ulceration of the auricle or external canal that does not heal within a few weeks is suggestive of cancer. For such lesions the use of various ointments over many months is to be condemned. These lesions are also insidious and grow very slowly. They tend to extend out of view beneath the skin of the auricle. In cases in which the external auditory canal or external meatus of the canal is involved, a radical mastoidectomy and excision of large portions of the auricle are essential for cure. An optimistic prognosis can be advanced with radical treatment in early cases.

In conclusion one can safely say that neoplasms of the ear, nose and throat are not as uncommon as is generally thought. Patients most frequently report their first symptoms and signs to the general practitioner. The cancer education program should help the physician shorten the time lag in establishing a diagnosis, but an improved cancer consciousness in all doctors is of primary value.

To reduce the period of delay in establishing a diagnosis the general practitioner, who is the most important cog in the wheels of the machinery set up to conquer this problem, must realize that cancer in the ear, nose and throat manifests itself in specific ways with many small significant signs and symptoms. On him falls much of the responsibility for early diagnosis and treatment that can mean a reduction in the mortality and morbidity from cancer.

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MEDICAL PROGRESS

SOME BIOLOGIC AND CLINICAL PROBLEMS RELATED TO INTRACELLULAR PARASITISM IN BRUCELLOSIS*

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THE intracellular localization of viable brucella organisms in the tissues of animals and human beings has been of fundamental interest ever since Bang[1] announced the etiology of contagious abortion in cattle in 1897. In this initial report from Bang's laboratory, clumps of intracellular bacilli were noted in the uterine exudate removed from a cow with threatened abortion. The intracellular localization of brucella did not appear to attract much attention for a number of years, and then some significant investigations were reported from the laboratory of Theobald Smith in the Department of Comparative Pathology at Harvard Medical School. In 1912 Fabyan[2] described with beautiful illustrative material the presence of brucella organisms within the tissue cells, and elaborated upon the histopathology of brucellosis in the guinea pig; this work did much to advance knowledge of the pathogenesis of brucellosis. Subsequently, in 1919, Smith[3] reported upon the localization of brucella within the epithelial cells of the bovine fetal membranes. He was impressed by the tremendous numbers of bacilli within the cells of the chorion, and illustrating his text with photomicrographs, he wrote, "Once in the cytoplasm the bacteria find it a favorable medium for multiplication and a protection against phagocytosis."

He continued as follows:

> The significance of this invasion of the chorionic epithelium from the standpoint of pathogenesis cannot be properly evaluated until a more complete history of the successive localizations of *Bacillus abortus* has been obtained. It is safe to assume that this particular cell parasitism is but one of a series of localizations and centers of multiplication in the fetal membranes although evidence points to it as perhaps the earliest stage in which the organisms gain by rapid, unchecked multiplication a considerable advantage over the host.

Goodpasture and his associates have more recently studied the mechanism of intracellular parasitism and have attempted to interpret the significance of their findings. Goodpasture[4] suggested that more precise information concerning the pathogenesis of infections could be obtained by study of the early invasion of chick-embryo tissues by micro-organisms. As a result of experimental observations with this technic he concluded in a provocative discussion that invading parasites could be divided into three main groups on the basis of their relation with the host cell[5]: the extracellular parasites, which appear to thrive best in an extracellular medium and include the gram-positive bacteria, *Streptococcus haemolyticus*, *Staphylococcus aureus* and *Diplococcus pneumoniae*‡; the facultative intracellular parasites, which include *Pasteurella tularensis*, *Brucella abortus* and *Past. pestis*‡; and, finally, the obligate intracellular parasites, which include the viruses. In a study of the tissue reactions that occurred early in the course of bacterial infections in the chick embryo, Goodpasture and Anderson[6] made observations with a strain of *Br. abortus*. They concluded that brucella organisms entered the ectodermal epithelial cells and proliferated there, and that if a cellular exudate did occur it was composed predominantly of mononuclear cells. Brucella appeared to be one of the bacterial species for which invasion of the cells of the host was actually favorable to the parasite. Phagocytosis might be deleterious to some bacteria, but it might actually be helpful in the attack of brucella upon the host. These observations were later confirmed and extended by Buddingh and Womack.[7] In studies carried out on patients with typhoid fever, Goodpasture[8] demonstrated that the organisms of *Salmonella typhosa* were located in and appeared to be proliferating within the young plasma cells in the lymphoid follicles of the intestines. This was later confirmed by Adams.[9] The observations and conclusions of Goodpasture[10] on the cell-parasite relation have stimulated considerable interest in the role of phagocytosis in bacterial infections, especially as related to gram-negative infections.

Castaneda[11] has studied the fate of brucella organisms in mice, guinea pigs and rabbits, and he also has concluded that an intracytoplasmic environment favors the multiplication of this species of bacteria. Organisms were found in many different types of cells, but he was not prepared to state what cell was most desirable for the metabolism of the brucella. Because few brucella cells were seen extracellularly, he believed that this site would not support growth very readily except in extracellular areas adjacent to tissue undergoing destruction.

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‡Classification of bacteria as used by Goodpasture.

Attempts to demonstrate intracellular brucella in the tissues of man have been unsuccessful except for the observation of Meyer,[12] who studied the organs of a patient who had had a severe and fatal infection with *Br. suis*. The patient died during the early phase of the disease. Meyer demonstrated clusters of bacteria having the appearance of brucella within the epithelial cells of the proximal tubules and glomerular capsule of the kidneys.

Relation of Intracellular Brucella to Duration of Disease and Outcome of Antibiotic Therapy

The interest of my associates and myself in intracellular parasitism by brucella has stemmed from two fundamental clinical problems. The first concerns the mechanism or mechanisms whereby brucellosis can exist as a chronic infection in animals and in man. The second was created by the failure of antibiotics to eradicate completely brucella from the tissues of some patients, and from experimentally or naturally infected animals.

Because considerable confusion has been created by the loose application of words and phrases to the natural course of brucellosis, it is necessary at the outset to make a brief excursion into semantics and define what is meant by "acute" and "chronic" brucellosis in human beings. Both terms imply that the patients are ill and have symptoms because of the presence of brucella in the tissues. Regardless of the severity of the symptoms, acute brucellosis has been defined as an illness that has endured for three months or less. Subacute brucellosis has indicated that symptoms have lasted from three to twelve months, and chronic brucellosis has referred to an illness of more than a year's duration. It must be emphasized that the presence of brucella organisms in the body does not necessarily mean a state of ill health, any more than the presence of virulent *Corynebacterium diphtheriae* or *Str. pyogenes* in the nasopharynx of healthy persons or the localization of *S. typhosa* in the gall bladders of healthy subjects. These persons are carriers of virulent and invasive pathogens. Both animals and man may harbor viable brucella cells in their tissues without symptoms, and should likewise be considered as *carriers* of brucella.

There is ample evidence that healthy-appearing animals may harbor and disseminate brucella organisms for years. Members of the Mediterranean Fever Commission on the island of Malta were quite amazed at the healthy appearance of goats that were shedding *Br. melitensis* in milk. This observation was forcefully recorded by Eyre and his associates[13] as follows:

> During the course of the investigations, perhaps the most striking observation recorded was the healthy appearance of the majority of the infected goats. The animals were sleek and plump, with smooth, healthy-looking coats; they took their food well, were as active as their uninfected fellows, and yielded as large a quantity of milk and of apparently as good a quality. Palpation failed to reveal any enlargement of lymphatic glands or of alteration of the mammary gland. In many instances the infected milch goats were the best looking and the best milkers in the herds, and in a few instances only it was noted that an infected animal suffered from a short barking cough at irregular intervals.

During a visit to the endemic centers of brucellosis in France and Italy in the summer of 1951, my attention was called to the same healthy appearance of sheep naturally infected with *Br. melitensis*. The predilection of the mammary gland for the localization of brucella was well established in the cow many years ago.[14-16] Apparently healthy cattle, with and without a history of previous abortions, may shed brucella in milk and udder secretions for months, and in some cases, for four to six years. Brucella may parasitize the tissues of swine with and without evidence of localization.[17, 18] Karlson and Boyd[19] reported that brucella may persist in the tissues of horses for long periods without evidence of disease. And, finally, small laboratory animals such as mice have been infected with sublethal doses of brucella. These animals have not manifested any evidence of illness, and after a lapse of more than a year brucella organisms have been isolated from the spleen, an observation that has also been made by Eddy.[20]

Although it is apparent that brucella can parasitize the tissues of animals without demonstrable harmful effects to their health, there is little similar information available for man. In a few cases brucella organisms have been isolated from the blood of patients after they had recovered from an acute attack of brucellosis, and at a time when they have maintained that they had no symptoms. The Mediterranean Fever Commission was likewise impressed with the paucity of symptoms in persons with evidence of bacteremia. In one study Shaw[21] investigated native laborers at the Naval Dockyard in Malta and isolated *Br. melitensis* from the blood and urine of persons who were working. In another study Shaw[22] was able to culture brucella from the urine in ambulatory patients at intervals of many months. Although it would be desirable to have more detailed information concerning the state of health of the subjects investigated by Shaw, it became apparent many years ago that the tissues of man could be parasitized by brucella with few or no localizing manifestations, and a minimum of symptoms of ill health. McVay and his group[23] stated that they had recovered brucella from the prostatic tissue of men without symptoms of brucellosis, but in a similar study carried out by O'Leary and Spink[24] in male patients with a history of definite exposure to infected animals and with immunologic evidence suggestive of invasion of the tissues by brucella, the organisms were not recovered in a single case. In view of the fact that the tissues of naturally infected animals may retain viable brucella for long periods without evidence of ill health, it is reasonable to assume that

man also participates in such a host-parasite relation, possibly more frequently than is appreciated, but precise evidence is needed to prove this thesis.

Changes Induced in Human Tissues by Brucella

Several years ago I became impressed not so much by the debilitating type of illness caused by brucella but by the lack of localizing complications in the majority of patients: they appeared ill and had a multiplicity of complaints, and yet they presented few or no physical abnormalities. It seemed likely that in spite of the lack of localized findings, these patients were ill because of the widespread dissemination of the brucella in the tissues. In an attempt to gain more information on the pathogenesis of brucellosis in human beings the changes that took place in the tissues of persons with bacteriologic evidence of disease were studied. A survey of the literature indicated that relatively few histopathologic studies had been carried out on post-mortem material. This scarcity of information was probably due to the low death rate in brucellosis. In my own experience over a period of fifteen years, only 3 patients out of over 200 have died because of brucellosis, and in these cases death was due to subacute bacterial endocarditis.

Because brucella organisms tend to localize in the reticuloendothelial tissues, it was decided to study, by means of biopsy technics, tissue obtained from the sternal bone marrow and the liver. Cervical and axillary lymph nodes were also excised. In 1 case the spleen was removed from a patient and studied. A survey of this material revealed a definite and characteristic pattern of tissue reaction, though by no means specific. In preparations of bone marrow, liver, lymph nodes and spleen removed from ambulatory patients, granulomatous lesions were readily seen. The outstanding features of this inflammatory reaction were the appearance of epithelioid cells, giant cells of the Langhans and foreign-body types, and a cellular infiltrate composed of lymphocytes, plasma cells and, occasionally, eosinophils.[25-27] Although sections were prepared with appropriate stains, in no case were bacteria compatible with brucella seen. On three occasions, *Br. abortus* was recovered from the aspirated bone marrow when simultaneous cultures of venous blood remained sterile. No brucella organisms were recovered from cultures of the hepatic tissue. However, follow-up studies in this clinic indicate that brucellosis may at least be a contributing factor in the genesis of cirrhosis of the liver, which is a view shared by others.[28, 29] It is to be emphasized that most of our studies have been carried out in patients with infections due to *Br. abortus*. Although such lesions reveal a minimum of necrosis, this species of brucella occasionally causes suppuration. However, suppuration of the soft tissues and bones is more likely to occur in infections due to *Br. suis*.

In addition to the foregoing tissue changes, disabling complications from localization of the brucella have been observed in several cases. The most commonly encountered complication has involved the skeletal system, especially the spine. Although clinical studies have been made in 8 patients with brucella spondylitis, there has been no opportunity to define the histopathology of the lesion. But Lowbeer[30] has detailed his post-mortem findings in 4 cases of brucella spondylitis. The outstanding features were a marked destruction of bone and its replacement by granulomatous tissue containing central caseous necrosis. There was a peripheral fibrotic encapsulation of the lesion, as well as evidence of rapid proliferation of bone with exostoses and intervertebral bridges. Although the process is suggestive of tuberculosis, histologically and roentgenologically, the lesion is usually self limiting, and the patient with brucellosis recovers much more rapidly with evidence of new-bone formation. I have also observed suppuration of the sacroiliac and hip joints from *Br. abortus*, and of the long bones from *Br. suis*. The second most common complication that I have seen is involvement of the peripheral and central nervous system. Four cases of encephalomeningitis have been reported.[31] Brucellosis causes chronic meningitis. In 1 patient, *Br. abortus* was isolated from the cerebrospinal fluid in July, 1947, and in April, 1949. Except for intermittent periods of fever, chills and headache, over a period of four years, the patient led a normal life. All patients recovered, and so the meningeal inflammation has not been studied histologically. Hansmann and Schenken[32] have reported a fatal case of meningoencephalitis due to *Br. suis* in which post-mortem examination showed thickening of the pia and arachnoid because of a proliferation of connective tissue and an inflammatory reaction consisting of lymphocytes, plasma cells and mononuclear cells. There was also a thickening of the meningeal vessels and a perivascular cellular reaction in the brain substance. A painful and incapacitating complication is due to involvement of the peripheral nerves, particularly the sciatic nerve. Radicular pain may or may not be associated with spondylitis. Subacute bacterial endocarditis has been another complication demonstrated in clinical material. Four cases, all caused by *Br. abortus*, have been studied; 3 patients died. The fourth patient recovered and has remained well for five years after treatment with streptomycin and sulfadiazine. Post-mortem studies carried out on the tissues of the patients dying of endocarditis did not reveal any of the characteristic granulomatous lesions.[33, 34] Two cases of orchitis have been seen and treated successfully.

Pathogenesis of Brucellosis in Experimentally Infected Animals

Although a review of the documented information on animal and human brucellosis and a neces-

sarily limited study of human material had revealed the general character of the tissue reactions, still more basic information about the genesis and ultimate fate of the lesion was desirable. More knowledge was needed concerning the host-parasite relation and the reason for the appearance of a granulomatous lesion without necrosis, or for the development of a suppurating lesion with destruction of tissue. Another question requiring an answer was that of the inflammation of the tissues induced by each of the three species of brucella. Did invasion of the tissues by the different species result in distinctive patterns of inflammatory reactions? What role did hypersensitivity play in the evolution of the tissue reactions? With more and more interest being manifested in the therapy of brucellosis with antibiotics, was it possible with these agents to eradicate the bacteria from their intracellular localization? To provide an answer to these and related problems, it was necessary to investigate the disease in experimentally infected animals.

If one records and then analyzes the clinical data on the nature of human illness provoked by each of the three species of brucella, one is impressed by the different patterns of disease induced by each of the species. In general, infections due to *Br. melitensis* result not only in incapacitating and debilitating complications but also in marked toxicity in the acutely ill patient. This toxemia is more distinctive for *Br. melitensis* than that caused by the other two species. *Br. suis* is much more likely to cause destructive and suppurating lesions resulting in a chronic form of illness. Disease caused by *Br. abortus* may reveal a toxic patient or one with serious complications, but the over-all clinical picture is a milder form of illness compared to that resulting from *Br. melitensis* or *Br. suis*. In view of these differences in the response of the patients to infection by each of these species, it was deemed important to study in detail the patterns of the tissue reactions in experimentally infected guinea pigs. This was carried out by Dr. A. I. Braude,[35] who selected a large group of brucella strains recently isolated from human patients, and then studied the response of the animals to infection with these strains. These observations closely paralleled the results that had been observed in human subjects. Practically every animal inoculated with *Br. suis* revealed the presence of abscesses involving especially the spleen, liver and testes. On the other hand, the abscesses caused by *Br. melitensis* were remarkably fewer in number, but the animals appeared sicker. Only a slight destruction of tissue was produced by *Br. abortus*, and the animals had only a mild illness. Subsequently, Braude[36] extended these observations in infected animals to the evolution and significance of the granuloma in brucellosis and the influence of a state of hypersensitivity on the appearance of this lesion. Because of the consistent appearance of lesions in the liver, the hepatic granuloma was selected for comparative study. His observations, which are a distinct contribution to knowledge of intracellular parasitism in brucellosis, may be summarized as follows: a few hours after the introduction of brucella into the body, the organisms appear within the cytoplasm of the circulating polymorphonuclear leukocytes; shortly thereafter, the blood stream is cleared of organisms, and the hepatic sinusoids reveal the presence of parasitized polymorphonuclear leukocytes, and the Kupffer cells also have brucella organisms within them. Within a matter of hours, the polymorphonuclear leukocytes begin to disappear, and there is a grouping of Kupffer cells with the contained organisms. The cellular aggregates increase in number, and with the simultaneous appearance of epithelioid cells intracellular and extracellular brucella organisms disappear. These cellular aggregates fuse to form a large granuloma composed mostly of epithelioid cells, and Langhans giant cells make their appearance along with hyaline changes in the center of the granuloma. The further elapse of time results in a diminution in the size of the granuloma and a reduction in the cellular inflammation around the lesion. Finally, in a few months the granuloma disappears without leaving a demonstrable scar. The evolution of the foregoing lesion is characteristic for *Br. abortus*. This pattern of reaction represents a good defense mechanism in which the intracellular and extracellular bacteria are disposed of successfully without tissue destruction, the mononuclear being the basic cell in this defense. The defense is not so successful against *Br. suis*. With the arrival of polymorphonuclear leukocytes and brucella in the hepatic sinusoids, there is not the appearance of epithelioid cells and a diminution in the number of bacteria but rather an accumulation of polymorphonuclear leukocytes, and the destruction of tissue, resulting in the formation of an abscess. This abscess may become walled off by fibrous tissue, but brucella organisms may reside within the lesion for long periods. By comparing animals displaying dermal hypersensitivity to brucella antigen with those that were desensitized, Braude could not detect any difference in the evolution of the granuloma. Hypersensitivity did not appear to influence the tissue reaction to viable brucella. This does not imply that hypersensitivity plays no role in the symptomatology of the patient with brucellosis.

Braude and his associates[37] have contributed further to knowledge of the host-parasite relation in brucellosis in studies carried out in swine. An investigation was undertaken in which the object was to establish a chronic infection in swine by the repeated injections of *Br. suis* over a period of many months. The idea was entertained that if a chronic inflammatory reaction were induced in the liver, cirrhosis might result. The strain of *Br. suis* used

was isolated from the blood of a seriously ill human patient. Injection of this strain into guinea pigs resulted in widespread suppurative lesions. Three hogs were injected intraperitoneally at monthly intervals for a year with a saline suspension of the entire culture from an agar slant. The amazing feature about this experiment was that the hogs tolerated the introduction of these large amounts of bacilli without any evidence of ill health. They gained weight as rapidly as the uninfected control, and no gross or microscopical lesions were observed in any of the tissues after death. That an infection had been established was proved by the marked elevation of agglutinins and the presence of a bacteremia. It became quite apparent that in the attempt to establish a porcine infection with demonstrable changes in the tissues, a naturally resistant strain of hogs had been encountered, an observation that had also been made by Cameron.[38]

Influence of Intracellular Parasitism in Brucellosis on the Outcome of Antibiotic Therapy

The successful application of the sulfonamides and antibiotics to the treatment of other infectious diseases prompted a series of investigations on the effects of these agents in experimental and human brucellosis. In the earlier observations studies were made in vitro, and later the chick embryo was utilized for the screening of the various drugs.[39-44] As a further refinement in the testing of agents in experimental brucellosis, the mouse was selected for study.[45] As a result of these investigations and their application to the therapy of human patients with brucellosis, some interesting and important aspects of the host-parasite relation were unfolded. It was observed that in vitro streptomycin had a rapid and lethal action on all strains of brucella tested. After this exposure of the organisms to streptomycin, only a few brucella cells remained viable, and these were found to be streptomycin-resistant variants. Although streptomycin appeared to be a highly efficacious agent as a result of in vitro experiments, when the drug was administered to human patients the results were disappointing. Only temporary improvement, if any, occurred. However, as a result of observations with a combination of streptomycin and sulfadiazine in the infected chick embryo, the results in human subjects were quite encouraging.[27, 46, 47] But even with this advance in therapy, failures occurred, and a significant number of patients relapsed. It became quite apparent that the brucella organisms were not being eradicated from the tissues. Another series of observations with aureomycin brought forth a biologic paradox. It was observed in vitro and in the infected chick embryo that aureomycin was much less efficient against brucella than the combination of streptomycin and sulfadiazine. After these observations, I was somewhat reluctant to use aureomycin in the therapy of human patients with brucellosis. My initial experience with aureomycin in the treatment of such patients was in Mexico City with Dr. Ruiz Castaneda. The combination of streptomycin and sulfadiazine proved to be too toxic in some of the Mexican patients seriously ill with infections due to *Br. melitensis*, and this afforded an opportunity to try aureomycin. Much to my surprise it was soon established that aureomycin was superior to streptomycin and sulfadiazine in these cases.[48, 49] That the introduction of the antibiotics has marked a definite advance in the therapy of human brucellosis is emphasized in a follow-up study of patients treated with these agents.[50] However, the adequate administration of these drugs was still followed by clinical and bacteriologic relapses in a number of patients. Heilman[51] had observed in mice infected with *Br. suis* that a combination of dihydrostreptomycin and aureomycin was a more effective therapeutic method than the use of either agent alone, or the use of dihydrostreptomycin and aureomycin. Herrell and Barber[52] applied these findings to the treatment of brucellosis in human beings and reported satisfactory results with the combination of dihydrostreptomycin and aureomycin. It is significant that in the experiments reported by Heilman this combination did not completely eradicate brucella organisms from the tissues.

The failure of the antibiotics to eradicate brucella from the tissues of infected animals and the relapse of human patients after treatment suggested that the intracellular location of the organisms protected the bacteria against the action of the drugs. Utilizing an in vitro technic Magoffin and Spink[53] demonstrated that when suspensions of intracellular and extracellular brucella were exposed to streptomycin alone, and in combination with aureomycin, terramycin or chloramphenicol, the leukocytes protected the organisms against the rapid lethal effect of these agents. Employing a different approach to the problem, Shaffer, Kucera and Spink[54] permitted phagocytosis of *Br. suis* to occur within the peritoneal cavity of the rat, and then the living leukocytes containing viable brucella organisms in their cytoplasm were removed, suspended in a synthetic tissue culture medium and exposed to various individual antibiotics and combinations of antibiotics. Under these circumstances the intracellular brucella organisms were protected against the lethal action of the drugs, whereas the extracellular bacteria were killed. Barski[55] had demonstrated with tissue-culture technics that intracellular tubercle bacilli were also protected against the action of streptomycin, whereas extracellular organisms were killed.

On the basis of the foregoing experimental studies, and as a result of clinical observations, it appeared that the antibiotics would control and exert a

suppressive action in brucellosis, but that complete eradication of the organisms from the tissues depended upon the defense mechanism of the host. Under these circumstances one could anticipate an occasional patient who would have a relapse or a protracted infection, even after the adequate administration of the most efficient combination of antibiotics now available. The interrelation of immunity and the suppressive action of drugs was explored further in mice in which sublethal brucella infections had been established.[56] When the animals were infected and then immediately treated with the individual antibiotics, or combinations of antibiotics, the infections were suppressed, but the organisms were not eradicated from the tissues. However, if the animals were infected and then several weeks were permitted to elapse before treatment was initiated, the brucella organisms were completely eradicated from the tissues when a combination of dihydrostreptomycin and aureomycin or terramycin was used. It was quite clear that in the interval that elapsed between the establishment of the infection and the start of treatment, the animals had developed an immunity, which, abetted by the suppressive action of the drugs, succeeded in eliminating the infection.

Efficacy of Cortisone and ACTH

Since several studies had shown that a basic host-parasite relation in brucellosis involves the intracellular localization of the bacteria and that brucella organisms in this position were protected against the antibrucella action of several antibiotics, further investigations were undertaken to determine if the parasitization of the cells of the host could be terminated by other means. Two possibilities presented themselves: other drugs or combinations of drugs might be found that could penetrate the cell wall of the host without harm and exert a deleterious effect upon the brucella (no significant progress has been made along this line to date); and a procedure suggested by observations that had been carried out in experimental tuberculosis. Hart and Rees[57] reported that the tubercle bacilli in mice with acute and chronic infections were disseminated in the tissues after the administration of cortisone. Brucellosis simulates tuberculosis in many respects. In both diseases the invading parasites localize within the macrophages and induce a granulomatous tissue reaction. Chronicity is a feature of both diseases, and bacterial hypersensitivity occurs in both. It was anticipated that the administration of cortisone to experimentally infected animals might result in the liberation of brucella from the cells, and then the extracellular organisms could be successfully attacked by antibiotics administered at the same time. In fact, human subjects with acute typhoid fever have been successfully treated with a combination of cortisone and chloramphenicol.[58, 59] In the initial approach to the brucella problem, observations were made with each of the three species of brucella in mice, guinea pigs and rabbits.[60] Infections were established in the animals after they had been pretreated with cortisone. The continued daily administration of cortisone to mice with an acute illness due to *Br. suis* resulted in a fulminating and fatal infection. The tissues, especially the liver, revealed widespread areas of necrosis, and there was a remarkable proliferation of brucella, not only in the macrophages but also in the parenchymal cells. These results with cortisone in the acutely ill animal were in marked contrast to those obtained in animals whose tissues had been parasitized by brucella over a period of many months.[61] In the chronically infected animals, cortisone depressed the dermal hypersensitivity to brucella antigen, but its administration did not appreciably alter the agglutination titer. But, more important, there was no demonstrable alteration in the brucella lesions, compared with the control material, and there was no evidence of multiplication and dissemination of brucella. Repeated observations indicated quite clearly that the response to cortisone was disastrous in animals with acute brucellosis, but the drug was without any demonstrable effect on the course of brucellosis in the chronically infected animal. Why did cortisone have no perceptible effect on the tissue lesions in the chronically infected animals? Up to the present time no entirely satisfactory answer has been presented. One possible explanation for the difference is that, in the chronic infection, the tissues are parasitized by relatively few organisms. Although a disturbance in the tissues might result from the cortisone, followed by the liberation of brucella from their intracellular position, an adequate immune mechanism might be present, which could ensure the immediate destruction of the bacilli, thus thwarting multiplication and preventing invasion and destruction of other tissue cells. This aspect of the problem is being pursued further.

The pattern of response to cortisone having been established in mice with acute and chronic brucella infections, it was decided to evaluate the results of adrenocorticotrophic hormone (ACTH)* in human subjects with chronic brucellosis.[62] A detailed statement on the definition of chronic brucellosis has been presented elsewhere.[63] To clarify what was attempted in the present study with ACTH, my concept of chronic brucellosis is briefly summarized. Chronic brucellosis may manifest itself in one of the following three ways: after an acute attack patients may have continued illness because of a relapsing and febrile illness; other patients may continue in poor health because of localization of the organisms, which is manifested by suppuration; and patients may be suffering from the residua of a previous acute illness, rather than from active infection. It

*Kindly supplied by the Armour Laboratories, Chicago, Illinois.

is the last group of patients that has given the most difficulty and to whom it was desired to administer ACTH. The first two groups with definite evidence of active infection respond to therapy with antibiotics. The symptoms of the third group usually consist of weakness, mental depression, nervousness, anorexia and vague somatic aches and pains. The antibiotics have not been of much value in the treatment of such symptoms. But it was thought that ACTH might alleviate the symptoms of mental and physical depression, and by altering favorably this pattern of symptomatology, make the patients continue to feel better after the administration of ACTH had been discontinued. Five patients with chronic illness have been treated and followed for a sufficient time to warrant conclusions about the effects of ACTH. Thus far, the results have not been outstanding one way or the other. Two patients appeared to be definitely improved while receiving ACTH, and have remained well for several months after treatment was discontinued. In 3 others, the administration of ACTH was followed by a relapse into the same monotony of complaints without convincing evidence of active disease.

Two patients having acute brucellosis have been treated at the time a bacteremia due to *Br. abortus* was demonstrated. The first patient had been ill for a month with fever. Coincident with the administration of ACTH the fever subsided, the bacteremia was no longer manifested, and the patient recovered completely; he has remained well for several months without a relapse. The second patient demonstrated a much more dramatic response to the hormone. He had been ill for two months, and when he entered the hospital he appeared critically ill with a high fever, and an enlarged and tender liver. Within twenty-four hours of the first dose of ACTH, he was converted from a toxic and listless patient into an alert and afebrile one with few residua of his toxicity. The pain in the liver subsided, and the organ became smaller. ACTH was administered for several days. During this time the patient felt well in spite of the fact that the bacteremia persisted. When the administration of ACTH was discontinued, he became febrile, and because of the bacteremia he was then treated with a combination of dihydrostreptomycin and aureomycin. He promptly recovered, and he has remained well for several months.

Although the number of patients treated with ACTH is not large, the present experience with 7 patients indicates that there is little to be gained in treating patients with the hormone who have the residual symptomatology many months or years after an acute attack of the disease. However, in the critically ill and toxic patient with acute brucellosis, ACTH might very well be employed for twenty-four to forty-eight hours, simultaneously with dihydrostreptomycin and aureomycin or terramycin.

Discussion

Brucellosis may be considered an example of what Theobald Smith[64] has called aberrant parasitism. The natural reservoir for the disease resides primarily in domestic animals; man becomes infected accidentally through either direct or indirect contact with diseased animals. Since the conclusion of World War II, there has been a concerted attempt to eradicate the disease from animals, and with this accomplished brucellosis will cease to exist as a disease in human beings. But brucellosis will be stamped out only after years of co-operative effort. In the meantime several basic problems of general biologic interest await solution. Pertinent to the discussion presented in this paper is the need for further study of the host-parasite relation in brucellosis. Why is the brucella species protected against lethal agents and against an unfavorable extracellular metabolic environment when it takes up a position within the host's cell? Investigations on intracellular metabolism, with particular reference to intracellular enzymatic activity, should provide valuable information. More precise data along this line should be of considerable aid in a more rational chemotherapeutic approach. Studies aimed at the nature of intracellular metabolic activity in a disease like brucellosis should be helpful in a better understanding not only of other bacterial infections but also with rickettsial and viral infections.

Several enigmatic problems that concern natural and acquired immunity in brucellosis await solution. One of the outstanding features of brucellosis is that young animals and young children tolerate brucella infections, and their tissues are even more resistant to invasion than those of adults. A distinguished veterinarian has recently discussed this biologic paradox and commented on the lack of knowledge to explain these differences.[65] More information is needed concerning the nature and efficiency of natural and acquired humoral immunity. Finally, few precise data are available on the role that bacterial hypersensitivity plays in the genesis of the clinical manifestations of brucellosis. This is of considerable practical importance since it is common practice to utilize brucella antigens in the therapy of human patients.

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MEDICAL INTELLIGENCE

AN EVALUATION OF A SIMPLE RAPID-SECTION TECHNIC FOR IMMEDIATE HISTOLOGIC DIAGNOSES*

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BOSTON

IN 1944 MacMahon[1] devised a simple method for the rapid sectioning of tissue that has displaced the common frozen-section technic from the hospital laboratories associated with the Department of Pathology of Tufts College Medical School. With this technic 590 histologic diagnoses have been established during operations in the New England Medical Center in the past three years. These diagnoses have been accurate in 97.6 per cent of cases, and, what is equally important, approximately 90 per cent of the diagnoses have been made by residents in training. From these results it seems that this simple diagnostic procedure might be considered reasonably reliable.

With the use of fresh tissue cut by hand with a safety-razor blade, the rapid-section technic is both quicker and easier than the frozen-section method. It permits multiple sections to be made in a few minutes, and obviates the artefacts created by freezing, so that adequate paraffin sections may be prepared from blocks already used to establish a working diagnosis at the time of operation. This rapid-section technic was not introduced into the routine of this laboratory until it had been found to be as reliable, in expert hands, as the more complex and more costly conventional methods.

Details of the rapid-section method have previously been outlined.‡ The essential equipment, which can be carried in one's pocket, consists of a glass slide covered on one side with a dry film of toluidine-blue dye; a safety-razor blade; a small watercolor brush (a match will suffice); and a clean slide and coverslip. The technic is as follows: a small section of fresh tissue 1.0 to 0.5 mm. in thickness is cut, and the stained slide is gently drawn across only one surface of the tissue until the tissue is uniformly stained; the stained section is immersed in water and then mounted in water with the stained side up for microscopical examination with a powerful light.

From 1949 through 1951, 590 of the 6535 surgical specimens (9 per cent) submitted to the Department of Pathology of the New England Medical Center were diagnosed at the time of operation by the rapid-section method (Table 1). Eleven of these diagnoses (1.9 per cent) were deferred until permanent paraffin sections could be studied, and 14 (2.4 per cent) were definitely erroneous. Among these 14 there were 6 positive diagnoses of cancer, giving an incidence of approximately 1.0 per cent to this grave kind of error.

The interpretation of rapid-section slides is more difficult than that of routine paraffin sections, although not more difficult than that of frozen sections. Consequently, this procedure should not be

TABLE 1. *Surgical Specimens Examined by the Rapid-Section Method.**

TISSUE	1949			1950			1951			TOTALS		
	NO. OF SPECIMENS	DEFERRED DIAGNOSIS	ERROR	NO. OF SPECIMENS	DEFERRED DIAGNOSIS	ERROR	NO. OF SPECIMENS	DEFERRED DIAGNOSIS	ERROR	NO. OF SPECIMENS	DEFERRED DIAGNOSIS	ERROR
Head, neck and oral cavity	4	0	0	8	0	0	19	1	0	31	1	0
Stomach and duodenum	0	0	0	7	1	0	12	0	0	19	1	0
Liver and biliary system	1	0	0	5	0	0	24	0	0	30	0	0
Pancreas	1	0	0	3	0	0	7	0	1	11	0	1
Colon	3	1	0	19	1	1	40	0	0	62	2	1
Breast	13	0	1	28	0	0	45	0	0	86	0	1
Lymph nodes	10	0	0	28	1	1	42	2	1	77	3	2
Miscellaneous primary tumors†	2	0	0	2	0	0	11	1	0	15	1	0
Miscellaneous biopsies†	4	0	0	25	0	1	27	0	1	56	0	2
Specimen submitted by neurosurgical service	4	0	0	35	0	0	29	0	1	68	0	1
Specimen submitted by thoracic service	8	0	0	19	0	1	16	0	1	43	0	2
Specimen submitted by gynecologic service	3	1	0	8	0	0	26	1	1	37	2	1
Specimen submitted by urologic service	3	0	0	19	1	0	23	0	2	45	1	2
Specimen submitted by bone and joint service	1	0	1	3	0	0	6	0	0	10	0	1
Total rapid sections	57	2	2	205	4	4	327	5	8	590	11	14
Total surgical specimens	1654			2190			2691			6535		
Percentage of rapid sections	3.4			9.4			12.2			9.0		
Percentage of deferred diagnoses		3.5			1.9			1.5			1.9	
Percentage of error			3.5			1.9			2.4			2.4

*When, from a single surgical operation, several different tissues were examined, each was counted separately; when several specimens from the same organ were examined, all were counted once.

†Submitted by general surgical service.

*Presented at the spring meeting of the New England Surgical Society, Boston, March 26, 1952.

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‡MacMahon, H. E., and DelVecho, S. B. Simple technic for rapid sectioning. *New Eng. J. Med.* 231:794, 1944.

employed by those who have not become experienced in its use. The rapid-section method cannot win acceptance until it has proved to be successful in the hands of others, but its simplicity and reliability may encourage others to try it.

SUMMARY

The advantages of a simple rapid-section technic for immediate histologic diagnoses are outlined.

Diagnoses by this method have been 97.6 per cent accurate in 590 histologic specimens studied, for the most part, by residents in training.

A PRACTICAL AID IN THE DETECTION OF CARDIAC HYPERTROPHY

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BOSTON

DETERMINING the presence or absence of enlargement is the first requirement in the physical examination of the heart. The final decision is subject to confirmation by fluoroscopy or by the 7-foot film, and skillful percussion should give closely corresponding outlines. But skill in percussion of heart outlines seems to have seriously deteriorated in recent decades, so that many practitioners are unable not only to draw an accurate outline of the heart and area of supracardiac dullness but also to decide with confidence whether the left border of dullness is within or outside the left midclavicular line.

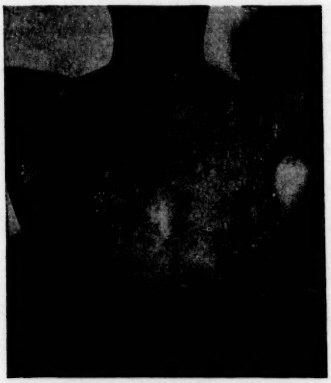

FIGURE 1. *Outline by Auscultation.*

In the presence of such doubts, the following approach gives results that correspond closely with skilled percussion and fluoroscopy and are based upon changes of sound sharper and more definite to the ordinary ear than those of unskilled (usually too heavy) percussion.

The patient, standing or sitting in erect posture, may continue to breathe naturally, although some care against forced inspiration and forced expiration should be taken. Then one places the stethoscope over the fifth left cartilage near the sternum and listens to the first sound, moving the stethoscope horizontally outward, 1 cm. at a time, toward the left axilla. Sooner or later, a sudden, quite marked lessening in the loudness of both sounds will be noted, and one should mark with a skin pencil† the point where the center of the stethoscope is when this change has occurred (Fig. 1).

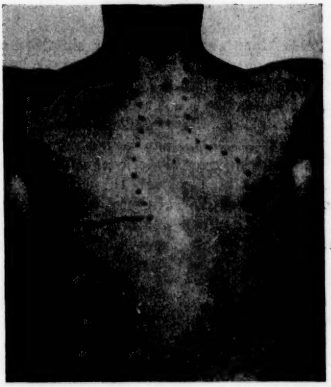

FIGURE 2. *Outline by Standard Light Percussion.*

This point will correspond closely to the left border of dullness in mid-respiration as determined by expert percussion, and if it is within the midclavicular line both enlargement and displacement to the left are excluded. The right border may be determined in the same manner, and the upper border, normally at the junction of the third left cartilage and the sternum. One must make sure that below the first point called the left border there is not further extension to the left in the fifth space and under the sixth rib from downward enlargement.

*Consulting physician, Boston City Hospital.

†A ladies' "eyebrow pencil" is best.

For thoroughness, the examiner who is not sure of his percussion will do well to mark multiple points to designate the center* of the stethoscope when the sounds seem to fall away, so as to form continuous outlines, right and left (Fig. 2).

If the upper border is lower than the third cartilage cardioptosis is present. If the left border in the fifth space is within the midclavicular line and then turns inward there is no hypertrophy or left displacement. If the left border does not turn inward until below the fifth space there is ptosis or hypertrophy of the left ventricle.

In certain cases in which the hearts have been known to have abnormal shapes, outlining by this method has shown surprising correspondence. It is not proposed, however, that this auscultatory outlining play any part in major cardiology. It is described here only in the hope that the busy practitioner who is not too sure of his percussion may find it a help, either by obtaining reassurance when he has feared abnormality or, more important, by being enabled to detect an abnormality that he might otherwise have missed.

*It is not clear why it should be the center and not the edge of the stethoscope that marks the significant loss of loudness but many observations show it to be true.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 38421

PRESENTATION OF CASE

A thirty-two-year-old woman was admitted to the hospital because of an enlarged liver.

Fifteen months before admission the patient had had a large ovarian cyst removed at another hospital; histologic diagnosis on the specimen was benign cystoma. She had done well postoperatively, but a month before admission, because of a few days of vaginal spotting before her menstrual period, she went to see her physician, who found a large mass in her abdomen. She had had no abdominal pain or gastrointestinal or urinary symptoms; her bowel habits were regular, and her appetite good; she had not lost any weight, nor was there any change in her well-being.

Thirteen years before admission she had had a number of attacks of "cystitis" that ceased after oral therapy and had not recurred. Five years before admission she had a subtotal thyroidectomy because of hyperthyroidism; at that admission no abdominal masses were noted. Subsequent to the operation the basal metabolic rate was −20 per cent, and since then she had taken thyroid medication. Three and a half years prior to entry at a routine periodic examination a firm lobular mass was palpated on the right side of the abdomen on bimanual examination; this was interpreted by the examiner as representing a ptotic right kidney. Three years before admission she was in the hospital for five days because of an acute anxiety state; examination at that time showed the palpable abdominal mass already mentioned and a firm nontender liver edge palpable 1 fingerbreadth below the right costal margin. She had been well in the interval, except that prior to the removal of the ovarian cyst she had had premenstrual spotting. There was no history of jaundice, alcoholism or exposure to toxic agents.

Physical examination revealed a well nourished woman in no acute distress. There was a well healed thyroidectomy scar. The breasts were normal. There were no skin tumors or enlarged lymph nodes. The lungs and heart were normal. The abdomen was soft and scaphoid and had a lower midline scar. The liver was enlarged, the lower border extending from the costal margin on the left to 4 or 5 fingerbreadths below the costal margin on the right and then swinging deep and descending to below the right anterior superior iliac spine. The surface of the liver was nodular, and there was an especially large nodule in the epigastrium. The spleen was not palpable. The right kidney could be felt separately posteriorly. Pelvic examination showed a normal uterus, a normal left ovary and a negative right vault. Rectal examination was negative.

The temperature was 99°F., the pulse 104, and the respirations 20. The blood pressure was 135 systolic, 90 diastolic.

The urine had a specific gravity of 1.022 and gave a + reaction for albumin; the sediment contained 75 white cells and 15 epithelial cells per high-power field. Examination of the blood showed a hemoglobin of 14.8 gm. and a white-cell count of 10,000, with a normal differential. The nonprotein nitrogen was 22 mg., the total protein 6.74 gm., the albumin 4.51 gm., and the globulin 2.23 gm. per 100 cc. The prothrombin time was 14 seconds (normal, 14 seconds), and the cephalin-flocculation test was + in twenty-four and forty-eight hours;

a bromsulfalein test disclosed 2 per cent retention of the dye. A stool gave a negative guaiac reaction. A roentgenogram of the chest was normal. An intravenous pyelogram showed the left kidney to be within normal limits in size, shape and position. The right kidney was low in position and displaced somewhat medially. Both the liver and spleen were enlarged, and the liver edge seemed to be superimposed on the iliac crest. After intravenous administration the dye was excreted promptly in good concentration on both sides. On the left side the calyxes, pelvis and ureter showed no abnormality, whereas on the right side there was slight blunting of the calyxes.

On the third day an operation was performed.

Differential Diagnosis

Dr. Briant L. Decker*: To summarize briefly, this thirty-two-year-old woman, who fifteen months previously had had a large, reportedly benign ovarian cystoma removed, fourteen months later was found to have a large, nodular liver. She had no complaints except premenstrual spotting, which had also been present before the removal of the cystoma. She had recurrent cystitis for thirteen years and a thyroidectomy for hyperthyroidism five years before admission. Three and a half and three years before admission she was found to have a mass in the right abdomen that was thought to be a ptotic kidney but was probably the cystoma. On admission the liver-function tests were negative, as were routine blood counts. The urine showed 1.022 specific gravity, + albumin and 75 white cells per high-power field.

May I see the x-ray films?

Dr. James J. McCort: As described in the protocol, the chest is normal; the lungs are clear, and the size of the heart is not unusual. There is no evidence of metastases. In the intravenous pyelogram the left kidney is normal in size, shape and position, excretes the dye well and shows normal cupping of the calyxes. The right kidney is displaced downward and medially by an enlarged liver; its calyxes and pelvis are slightly dilated, which may be the result of a previous infection or of kinking of the ureter from the downward displacement. The roof of the bladder is depressed by the body of the uterus, whose size is at the upper limits of normal. The bladder also shows a slightly prominent trabeculation.

Dr. Decker: Is there anything about the right kidney that might suggest carcinoma or a tumor?

Dr. McCort: Although the kidney is partially obscured by the downward extension of the liver edge, I can see no definite tumor in relation to it.

Dr. Decker: To me the large nodular liver with normal laboratory findings means metastatic carcinoma. A condition that may be mistaken for this, however, is primary carcinoma of the liver, either hepatoma or bile-duct carcinoma. With the former I would certainly expect evidence of cirrhosis, which was not present here; with the latter, cirrhosis is present in about 50 per cent of cases, and there should certainly be jaundice. Gummas of the liver are sometimes mistaken for metastatic carcinoma; there is no serologic report in the protocol. Echinococcus cysts are usually single and large. Congenital cysts of the liver are usually small and are frequently associated with polycystic kidney disease, of which there was no evidence; furthermore, an apparently normal liver edge was felt three years previously. Lymphoma usually invades the organ diffusely rather than by nodules. There was some enlargement of the spleen on examination, although it could not be felt. The question of hyperthyroidism raises the possibility of cancer of the thyroid gland, but I think that is extremely unlikely. Examination of the neck was negative; there was no evidence of metastases in the lungs or bones.

Of course, the question I should like to settle is the origin of the carcinoma, but I am not at all certain that I can. My first inclination, and perhaps the best possibility, is to blame the cystoma. I do not know the type of cystoma. I am told that it was large and benign. According to the description, it was most probably a simple smooth-walled cyst — a serous cystadenoma or a pseudomucinous cystadenoma. The latter, however, is usually found in much older women. It was apparently not of the papillary variety, or I am sure we would have been told so. Occasionally, although a cystoma may be reported microscopically as benign, it turns out to be malignant; in that case, I should expect a different train of events. I should expect that the patient would have peritoneal metastases or implants, with, most probably, ascites, abdominal symptoms, cramps and so forth.

The other important origin to be considered is the area drained by the portal system — that is, the gastrointestinal tract. Almost half the metastatic carcinomas of the liver arise from this area. However, I do not have the benefit of proctoscopic examination, barium-enema examination or a gastrointestinal series. I do have the report of a negative rectal examination and one negative stool guaiac reaction, and there were no symptoms referable to the gastrointestinal tract. The gastrointestinal tract is probably an important possibility.

In about 15 per cent of cases of metastatic carcinoma of the liver, the origin of the tumor is the genitourinary tract. The intravenous pyelogram is not suggestive of tumor; it seems that the right kidney was displaced downward and medially by the enlarged liver. There was no hematuria and no metastases in the lungs or long bones as might have been expected with a carcinoma of the kidney. I should expect liver metastases to occur later. Carcinoma of the body of the uterus or the fundus must certainly be considered. Although there was

*Assistant physician, Massachusetts General Hospital.

premenstrual spotting before and after the cystoma was removed, pelvic examination was negative. I should expect by the usual mode of spreading — direct extension — that something abnormal would have been felt in the pelvis. Dr. McCort makes me a little more reluctant to give that up as a possibility because he has mentioned that the uterus was at the upper limits of normal in size. With carcinoma of the fundus, I think metastases to the liver would occur much later.

Carcinoma of the upper respiratory tract or of the lungs comprises a small percentage of metastatic carcinoma to the liver. There was no evidence for the presence of either of these. Melanoma should be mentioned as a possibility, but likewise there was no evidence of its presence. A missed carcinoma of the breast, I believe, is unlikely.

I have just about talked myself out of all the diagnoses, but I suppose, with the evidence at hand, that the most reasonable diagnosis to make is metastatic carcinoma of the liver that originated in malignant degeneration of a cystoma. However, I realize that this patient may have had a silent carcinoma in either the stomach or the rectosigmoid region. I believe the operation was an exploratory laparotomy to make a diagnosis.

Dr. John B. Stanbury: This patient was extremely apprehensive before this episode. One can imagine her state when she arrived here, after her family physician had told her she had a large mass in the abdomen. We thought, much as Dr. Decker did, that the operation in the other hospital probably was for a disease that was now responsible for metastatic disease of the liver. We got in touch with Dr. Arthur T. Hertig, the pathologist who had examined the slides originally; he reported that it was a benign cyst. Rather than subject the patient to all sorts of laboratory tests and x-ray examinations we decided to make a needle biopsy of the localized mass.

Dr. Howard Ulfelder: I was asked to see the patient because of a possible connection between the gynecologic operation a few months previously and the present mass, but I could find no such connection. The examination was entirely negative except for the liver. I had no theory about what the mass might have been before the operation.

Dr. Edgar Taft: The exploratory operation was a needle biopsy of the liver. Dr. Daniel S. Ellis, unfortunately, is not here to tell us about what was found. However, when Dr. Ellis punctured the epigastric nodule he got back clear straw-colored fluid, and the nodule disappeared. Would this suggest another diagnosis to you, Dr. Decker?

Dr. Decker: Were other nodules aspirated too?

Dr. Stanbury: I could not delineate other nodules.

Dr. Decker: This was certainly a cyst of some sort.

Clinical Diagnosis

?Metastatic carcinoma of liver.

Dr. Decker's Diagnosis

Metastatic carcinoma of liver, from cystoma of ovary.

Anatomical Diagnosis

Polycystic disease of liver.

Pathological Discussion

Dr. Taft: Dr. Ellis wrote in the record that before he first inserted the needle in this patient's liver he had assumed that it contained metastatic carcinoma and that he might be able to establish a diagnosis. When he recovered only fluid at the first attempt, he made a second biopsy and thought he had recovered blood without liver tissue. There was liver tissue on section, however, but without diagnostic abnormality. He went back the next day and tried again. He said that the liver was much more firm and gritty than he would have expected with carcinoma. In the meantime he had begun to suspect that what she had was cystic disease of the liver, and the microscopical sections of the second specimen did show a cyst (Fig. 1). There was some dense fibrous tissue as well, which would be consistent with the wall of a fairly large cyst. This small cyst was lined by cuboidal epi-

Figure 1.

thelium, which is quite characteristic of the disease. Polycystic disease of the liver is rare and is associated with polycystic disease of the kidneys in from 30 to 88 per cent of cases, depending on which paper is read.[1] I believe there is some suggestion in the record that the patient had a polycystic right kidney although it is unusual to have one kidney affected and the other one normal. This disease is thought to be usually of congenital origin and is quite benign, as in this patient, who has had no further symptoms.

One article suggests[1] that the disease never results in liver failure, but I have read of several cases[2] and we have had one here, in which eventually the liver did begin to fail, as with polycystic disease of the kidney, and the patient finally died as the result of the disease.

DR. STANBURY: I have seen the patient under discussion quite recently, and she is well.

DR. THOMAS PAINE: Was there any connection between that and the ovarian cyst removed in the other hospital?

DR. TAFT: Not as far as I know. Such tumors metastasize throughout the peritoneum with peritoneal implants.

DR. ULFELDER: We have seen cases of carcinomatosis of the peritoneum in which sections of the liver showed tumor deep inside, but whether there had been actual infiltration from the peritoneum or metastases, I do not think anyone can say. Late in the game, one sees parenchymal liver metastases from carcinoma of the ovary.

DR. TAFT: Usually, from solid ovarian carcinoma.

DR. ULFELDER: Yes.

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CASE 38422

PRESENTATION OF CASE

A fifty-seven-year-old man was admitted to the hospital because of confusion and weakness.

The patient was well, active and alert until approximately three and a half months prior to admission, when he began to complain of moderately severe, constant, left midthoracic and paraspinal pain that radiated up and down the spine and was increased by local pressure, motion and prolonged sitting. Three months before admission generalized weakness and nervousness and moderate occipital and neck pain, with slight tenderness in this region, developed. About one and a half months prior to entry when the patient was in another hospital for a short time, allegedly he was told that he had bronchial asthma and that x-ray films of the spine showed "arthritis" and that those of the stomach were normal. His general health failed gradually; he had increasing asthenia, anorexia, nervousness and aches in his neck and back, and became confused and irritable. Three weeks before entry, an ache in the lower back that radiated into both hips and legs developed. Examination at another hospital one week prior to admission revealed generalized weakness, bloody spinal fluid, stiff neck, absent reflexes and weakness in the legs. The confusion and irritability gradually became more severe.

There was no history of injury, localized headache, unconsciousness, convulsions, chills, fever, visual disturbances, cough, hemoptysis, dyspnea or gastrointestinal or urinary symptoms. He had lost 25 pounds in weight in the three and a half months prior to entry.

Physical examination disclosed a dehydrated, agitated, overactive man, who appeared chronically ill and complained of neck pain. The mucous membrane of the mouth was red, dry and crusted and the tongue was black. The neck veins were flat. The heart size was within normal limits; there was a Grade I apical systolic murmur. The abdomen was soft, and there were no palpable organs or masses. The prostate was slightly enlarged but was not hard or nodular. There was marked nuchal rigidity, with marked pain on attempted flexion and tenderness on palpation of spinous processes in the neck and lumbar region. The patient followed most commands well but could only speak a few incoherent words in a simple way. The pupils were equal and regular and reacted to light and on accommodation. The optic disks were blurred bilaterally; there were no hemorrhages or exudates. There was a suggestion of weakness of both lower facial nerves. In response to the command to close his eyes, the eyes would roll upward; he was able to follow objects without any apparent difficulty. The corneal reflex was absent. The gag reflex was present. His hands were tremulous and moved in a random twitching manner. The strength in the arms appeared slightly diminished, and the deep tendon reflexes were present and equal. He was unable to perform adequately the finger-to-nose test. The abdominal reflexes were present. There was a suggestion of weakness of the right leg, although he was able to move both legs. There were absent reflexes in the lower extremities, and the plantar reflexes were flexor. He claimed to feel vibrations and seemed to be able to note position correctly. Examination of the sensory system was unsatisfactory.

The urine gave a + reaction for albumin. Examination of the blood revealed a hemoglobin of 15 gm. and a white-cell count of 9800, with 80 per cent neutrophils. The nonprotein nitrogen was 32 mg., the bilirubin 0.3 mg. direct and 0.7 mg. total and the total protein 5.30 gm. per 100 cc., with an albumin-globulin ratio of 1.9; the serum sodium was 152.2 milliequiv., the chloride 116 milliequiv., the

potassium 3.8 milliequiv., and the carbon dioxide 26.5 milliequiv. per liter. Lumbar puncture revealed clear, yellow spinal fluid under an initial pressure equivalent to 250 mm. of water; the fluid contained 500 mg. per 100 cc. of protein, 10 mg. per 100 cc. of sugar and 126 milliequiv. per liter of chloride and 145 red cells and 52 white cells (almost all mononuclear cells) per cubic millimeter. The colloidal-gold curve was 0001112222, and the spinal-fluid and blood Hinton tests were negative. A smear of the spinal fluid showed no organisms or acid-fast bacilli, and a culture yielded no growth. Roentgenograms of the chest demonstrated a

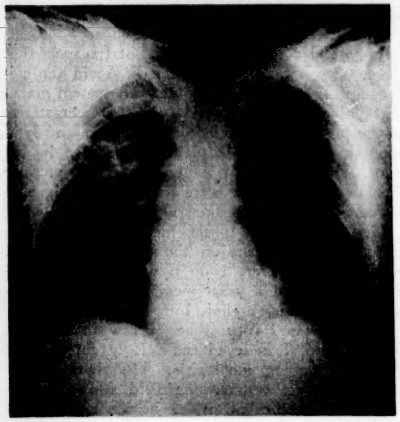

FIGURE 1.

homogeneous density in the right first interspace lying somewhat posteriorly, and narrowing of the trachea just above the clavicle (Fig. 1).

The patient was placed on fluids parenterally, streptomycin and PAS (para-aminosalycylic acid). There was little change in his condition, and the temperature remained elevated, varying between 101 and 103°F. On the sixth hospital day a lumbar puncture showed an initial spinal-fluid pressure equivalent to 600 mm. of water; the fluid was slightly xanthochromic and contained 110 cells per cubic millimeter, of which 28 were red cells and the rest large granular cells. The fluid contained 166 mg. per 100 cc. of protein, 28 mg. per 100 cc. of sugar and 106 milliequiv. per liter of chloride. The patient remained confused and semicomatose and refused oral feedings and medication. He gradually became comatose, and opisthotonos developed; there was no other definite change in the physical findings. He died on the fourteenth day.

DIFFERENTIAL DIAGNOSIS

DR. GARDNER QUARTON*: May I see the x-ray films?

DR. STANLEY M. WYMAN: A quite homogeneous, rather irregular density is present in the right-upper-lung field, probably in the posterior portion of the lung (Fig. 1). The trachea on the right is indented probably by some intrinsic pressure on its right aspect just above the clavicle. Otherwise, I do not see anything abnormal.

DR. QUARTON: This patient obviously had disease in at least two places: in the central nervous system, certainly in the meninges, and in the chest. The course of the illness, with the insidious onset and gradual increase in symptoms, suggests either neoplasm or infectious disease that began gradually and proceeded to death, which was apparently almost inevitable.

He had a great many findings and symptoms, some of which may be important and many of which are really difficult to interpret. The pain in the left midthoracic region, since the finding in the chest was on the right, I should suppose was not due to the condition in the chest but was referred pain. It is interesting that he was told that he had bronchial asthma. One wonders whether the findings in the chest were responsible for the symptoms that led to that diagnosis. The pain in the lower back, I do not believe can be explained at this point. The bloody spinal fluid that was found in the other hospital is difficult to interpret and may have been due to a traumatic tap. It would be helpful to know what the findings were in that spinal fluid. I think the negative statements are also interesting: he had no chills or fever, cough or hemoptysis. The 25-pound weight loss is consistent with a progressive neoplastic disease or illness of infectious type. Physical examination revealed definite signs of meningeal irritation — nuchal rigidity and tenderness on palpation in the neck and in the lumbar region. There was some evidence of increased intracranial pressure: the optic disks were blurred, and the cerebrospinal-fluid pressure was elevated, but not extremely elevated.

There seems to have been no convincing evidence for involvement of the long tracts of the nervous system that would help me in localization of parenchymal disease. The incoherence of speech, the disturbance in behavior and the gradually progressing disorientation suggest some generalized process, probably involving the cortex; they could equally well have been due to tumor within the brain. The weakness of both lower facial nerves was merely questionable. There was nothing else to suggest trouble with the upper motor neurons, so that I am going to disregard that. The rolling of the eyes upward is physiologic but is often seen in patients with peripheral seventh-nerve lesions; yet

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there were no other signs of seventh-nerve involvement. I shall assume that there was some seventh-nerve weakness but that it was not really conclusive. The corneal reflex was absent; there was no other evidence of fifth-nerve difficulty. The other superficial reflexes — the gag reflex and the abdominal reflex — were present. The absence of the corneal reflexes may have been due to the general disturbance in consciousness. The disappearance of strength in the arms and to some extent the weakness of the legs suggest involvement of the motor system, but there was no definite evidence of a paralysis. The difficulty in performing the finger-to-nose test could have been due to a general lack of co-operation. On the other hand all those findings could have been due to trouble within the brain or within the cerebellum. The fact that the reflexes were present in the upper and absent in the lower extremities suggests some kind of disease in the nerve roots to the lower extremities. The fact that the plantar reflexes were flexor, however, suggests that the long tracts of the spinal cord were not significantly involved. So does the apparent ability to note position and vibration.

The laboratory findings are interesting. The hemoglobin was normal, and the white-cell count was not suggestive of an acute infectious disease. The nonprotein nitrogen was within normal limits, the bilirubin not very abnormal, the total protein somewhat low, the sodium and chloride slightly high, and the carbon dioxide normal. The patient was not seriously dehydrated, although his tongue was dry. The most interesting and most important laboratory findings were the spinal-fluid findings. The cerebrospinal-fluid pressure was definitely increased, the protein high (500 mg. per 100 cc.), the sugar unusually low, and the chloride high but consistent with the serum chloride; the fluid contained abnormal cells, chiefly mononuclear cells. Those findings indicate a meningeal reaction, and the problem is a differential diagnosis among certain types of meningitis.

One should consider and discard syphilitic infection. The Hinton test was negative, and the colloidal-gold test was not consistent with syphilis. Tuberculous meningitis is a strong possibility. I am not clear enough about the signs in the chest to say whether they were consistent with tuberculosis. Both the clinical course and the diffuse pain could be explained by a chronic meningitic process of the tuberculous type.

I also have to consider very strongly yeast meningitis. I forgot to mention the black tongue — the patient could have had yeast on the tongue. In the meninges, torula would be the most likely candidate and could also account for a granulomatous process in the lung and the mass pressing on the trachea. I shall not mention the other rather rare yeasts and molds because I do not know of any way of making a differential diagnosis.

Weil's disease occasionally produces a lymphocytic meningitis, sometimes without jaundice, but I think it is very unlikely in this case. Tumors within the nervous system, involving the meninges, sometimes produce a picture simulating meningitis, — ependymomas metastatic to the meninges, — but as a rule the history and clinical picture are quite different; furthermore, there was evidence of disease outside the nervous system so I do not have to consider that.

So-called tumor meningitis — sarcomatosis, tumor arising from the cells of the meninges and spreading widely throughout the spinal fluid — is a possibility. This can produce a high spinal-fluid protein. I am not sure what the sugar would be. I suppose glycolysis could occur, but I suspect that the low sugar favors a meningitis. Again the evidence of disease outside the nervous system makes that unlikely. There are tumors that metastasize to the meninges — carcinomas, sarcomas and lymphomas; they would explain the disease in the chest. I am not sure whether they would produce the low sugar. There were no localizing signs to indicate another site in the body for tumor.

My diagnosis is torula meningitis, with the granulomatous lesions on the same basis as the meningitis; however, I do not think I can distinguish between a yeast meningitis and a tuberculous meningitis on clinical grounds.

Dr. Thomas Paine: When I saw this patient on the ward, I believed the history suggested a slowly developing meningitis. The signs of disease in the right-upper-lung field and the lymphocytes and the low sugar in the spinal fluid obligated us to treat him as though he had tuberculous meningitis; that is why he was put on streptomycin and PAS. Another possibility that was considered was tumor in the right-upper-lung field, with secondary infection, both of which had metastasized to the central nervous system.

Dr. Robert E. Schwab: I favored tuberculous meningitis, but I considered the other forms of meningeal reaction and carcinomatosis. We considered torula, but the cultures were negative and so we eliminated that. As I remember, we planted it on ordinary media, in which the organisms will grow out late and on Sabouraud's medium; both cultures were negative.

Dr. John B. Stanbury: I am surprised that the mass in the trachea was not felt.

Dr. Wyman: It is not very large; it is quite low and close to the clavicle. It would be difficult to palpate.

Clinical Diagnoses

Tuberculous meningitis.

Tuberculosis of lung.

Dr. Quarton's Diagnoses

Torula meningitis.
Torula infection of lung.

Anatomical Diagnosis

Adenocarcinoma of lung, with metastases to meninges.

Pathological Discussion

Dr. Benjamin Castleman: Autopsy showed a primary adenocarcinoma in the superior bronchus of the right upper lobe that had metastasized to the regional lymph nodes in the hilar area; one large lymph node accounted for the x-ray picture of tracheal indentation. There was also a metastasis on the pleura and in one of the adrenal glands. If some of the spinal fluid had been sent to the cytology laboratory, tumor cells might have been picked up, because, as Dr. Richardson will describe, there was involvement of the meninges.

Dr. Raymond D. Adams: I believe Miss Eulalia Grzebieniowska saw them in the spinal fluid.

Dr. Edward P. Richardson, Jr.: At autopsy we found diffuse carcinomatosis of the meninges generally. It appeared as a diffuse thickening of the pia arachnoid to the extent that the normal landmarks of the spinal cord, base of the brain, cerebellum and sulci of the convexities of the cerebral hemispheres were somewhat obscured.

Microscopical examination showed large numbers of typical carcinoma cells presenting as clusters, small clumps and gland-like structures, indicating that this was an adenocarcinoma. The most severe involvement was in the meninges overlying the cerebellum, where tumor cells accompanied the vascular adventitia into the substance of the cerebellum and formed a few small clusters of cells within the cerebellar cortex. Otherwise, there was no parenchymal involvement of the central nervous system.

Dr. Charles S. Kubik: Was the seventh nerve affected?

Dr. Richardson: The nerve roots generally were infiltrated by adenocarcinoma.

Dr. Schwab: A number of such cases were reported at the spring meeting of the American Neurological Association.[1] In a large percentage of those cases the sugar was at the level noted in the case under discussion.

Dr. Adams: We have observed several cases of carcinomatosis of the meninges like this one, in which the cerebrospinal-fluid sugar was too low to read. The three possible explanations of a subacute meningitis with low sugar are torula or some other fungus, tuberculosis and carcinomatosis. This patient's clinical course was unusually long for tuberculosis.

Dr. Quarton: How often do you find the organisms of torula in the spinal fluid?

Dr. Adams: Usually, they can be easily identified in a smear of the spinal fluid; sometimes, the fluid contains huge numbers of organisms. In 1 case we could not find them in repeated smears or isolate them by repeated culture, and yet at autopsy they could be seen in small numbers in the meningeal exudate.

Dr. Robert L. Berg: Why is the sugar so low?

Dr. Adams: I think it is because of the enormous number of cells. Merritt and Fremont-Smith[2] demonstrated years ago that inflammatory cells lower the sugar. Perhaps, too, neoplastic cells contain more glycolytic ferments and if present in large numbers will reduce the sugar content.

Dr. H. E. Marks: How high does the protein have to be in the spinal fluid to be pathognomonic of tumor?

Dr. Richardson: A high protein alone is not pathognomonic; both neoplasm and inflammatory disease can raise the spinal-fluid protein quite high. One would have to be guided by the cytology and other components of the fluid.

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OCTOBER COUNCIL MEETING

PEACE brooded over 8 Fenway, Boston, on October 1, 1952, on the occasion of the shortest and one of the best attended meetings of the Council of the Massachusetts Medical Society in the recollection of councilors now living. No particularly controversial subjects appeared to demand the application of any degree of heat, and the pyrotechnics that were displayed were of lesser magnitude and short duration.

Dr. Robert W. Buck was nominated by the President to serve as secretary *pro tempore* until the next regular election of officers, and this excellent choice was promptly confirmed by the Council.

The resolution of Norfolk District asking the Council to request Blue Cross "to write all its new contracts in such a manner as to include only insurable hospital services and to exclude all medical services" was rejected on the recommendation of the Committee on Blue Cross—Blue Shield Problems and the Executive Committee. Such a move was considered unnecessary at the present time because of the progress being made by the Committee on Hospital and Professional Relations in finding a solution for this vexing problem.

Several proposed amendments to the By-laws, one of the most important of which pertained to the method of selecting delegates to the American Medical Association, were referred back to the Committee on By-laws and Council Rules for further study.

The establishment of the Postgraduate Medical Institute was approved, with the implied understanding that its status in relation to the Society will be a matter of gradual evolution. The Council appropriated $2,000 toward its support for the fiscal year. Hopes that the Institute may become self-supporting are justified by the fact that its program for the 1952–1953 season is already oversubscribed, more than 200 physicians having eagerly joined the course and paid the $50 tuition fee.

Under new business the suggestion that a committee be appointed to study the desirability of state legislation to make fee-splitting and "kick backs" illegal was referred to the Committee on State Legislation. The same committee again had referred to it the recurrent matter of periodic registration of physicians. The efforts at organizing the medical profession for civil defense have once more disclosed the dismal ignorance that exists regarding the numbers and names of physicians not members of the Massachusetts Medical Society currently licensed to practice medicine within the Commonwealth. There are those who appear to believe that reasonably accurate information on this presumably vital subject represents not regimentation but common sense.

AMENDING THE UNION HEALTH DEPARTMENT LAW

THE bill introduced in the legislature by the Massachusetts Central Health Council, which, on its enactment, became Chapter 622 of the Acts of 1949, relative to the organization of union health

departments, has aroused a degree of opposition quite unexpected to its sponsors. This resistance has been based apparently on the supposition that the act will promote socialized medicine, jeopardize private practice or result in increased if not unwarranted costs in the maintenance of health departments.

It is difficult to determine how great this opposition is, although it has been at least sufficient to cause the Council of the Massachusetts Medical Society to ask for further study of the act by a special subcommittee of the Committee on Public Health.

The Central Health Council also is desirous of making the law as generally acceptable as possible to the medical profession and the people of Massachusetts. Massachusetts, as it happens, is one of the few states in the union without a functioning union-health-department system — most of those in other states are organized on county lines — and, incidentally, it is one of the very few states that do not subsidize part of the cost of local health services.

In an earnest attempt to make the act acceptable to all including those who have objected to certain details, a special committee of the Health Council has been studying it with a view to its amendment, and is prepared to present several changes designed to improve its reception without impairing its value as a public-health measure. As part of this re-drafting of the law the determination of the qualifications of directors of union health departments, whether physicians with public-health training or adequately trained lay persons, is removed from the Department of Public Health, where it at present resides, and is specifically outlined in the law itself. Changes are made in the representation of member municipalities on union boards of health, to give a larger voice to smaller communities, and formulas are prescribed for the apportionment of costs, by methods to be selected by the representative boards themselves. Another amendment provides for the transfer to the union health department, without impairment of status, of full-time incumbents of any office brought under the union at the time of its formation.

Since compliance with a law requiring the cooperation of communities rather than of persons can be obtained more agreeably by subsidy than in any other way, a bill is being framed that will ask for subsidies in this case. If it is accepted by the legislature, the unpopular factor of compulsion can be removed.

To many students of the union-health-department principle such a law, properly framed, represents not a deceitful contrivance to plunge the Commonwealth into the abyss of socialized medicine, but rather a further defense against socialized medicine by keeping in the custody of the community the organized protection of the public health at the community level. A common belief exists, possibly with some basis, that lack of progress represents not equilibrium but regression; a return to the ineffective permissive law of 1929, which has been suggested, would be a most discouraging acceptance of a reactionary policy.

One of the obstacles in the way of a more enthusiastic reception of the union-health-department principle is that the need for better public health is not as obvious as it once was — thanks to progressive practitioners of medicine and alert departments of health, and their mutually co-operative efforts. Neither is the need for a compulsory vaccination law particularly obvious in this enlightened day; but who in his right mind would wish to have such laws repealed?

Rather than permitting to be abandoned the patently sound principles on which the union health department act of 1949 is constructed, the act should now be so amended — and supported after amendment — as to become both generally acceptable and effective in practice.

GEORGE R. MINOT LECTURESHIP

It seems appropriate that the first George R. Minot Lecture, published elsewhere in this issue of the *Journal*, should have been delivered by Dr. William B. Castle, the late Dr. Minot's associate, friend and successor as professor of medicine at Harvard Medical School and director of the Thorndike Memorial Laboratory at Boston City Hospital. The lectureship was established in 1949 by the Section on Experimental Medicine and Therapeutics of the American Medical Association as a tribute to an American who has made an outstanding contribu-

tion to the development of clinical investigation and therapeutics. The first lecture, by Dr. Castle, was delivered in 1951, and the second, by Dr. Cyrus C. Sturgis, of the University of Michigan Medical School, in 1952; in 1953 Dr. Chester S. Keefer, of Boston, will give the third lecture.

Dr. Castle's paper traces Dr. Minot's career from his early years as a house officer at the Massachusetts General Hospital to his exceptional achievements in the investigation of diseases of the blood. The climax of his efforts was the discovery, with Dr. William P. Murphy, of the successful treatment of pernicious anemia — a contribution rewarded by the Nobel Prize in 1934. The lecture is expressed in terms of admiration and affection that honor both the subject and the lecturer himself.

During his lifetime Dr. Minot received numerous tributes for his work in the clinical evaluation of erythropoiesis, the nature of the anemias of scurvy and iron deficiency, the cause of alcoholic polyneuritis, the pathologic physiology of purpura, hemophilia and other hemorrhagic diseases, the natural history of leukemia and the effect of treatment in leukemia. In addition to the Nobel Prize he was the recipient of the Kober Gold Medal of the Association of American Physicians, the Gold Medal of the National Institute of Social Sciences, the Moxon Medal of the Royal College of Physicians of London and the Distinguished Service Award of the American Medical Association. Perhaps none of these was more appreciated than the lectureship bearing his name — an honor made possible by the contributions of his former students.

The George R. Minot lectures, and the devotion to medical science that they commemorate, should ever be a source of inspiration to those who follow him, not only as investigators in the special field of hematology but also as workers in clinical medicine in general. His achievements justify the respect paid his memory, the measure of the reverence that thoughtful men hold for the great man and the great physician.

1953 PRIZE-ESSAY COMPETITION

THE *Journal*'s prize-essay competition, open to fourth-year medical students in any school approved by the Council on Medical Education and Hospitals of the American Medical Association, is now open to members of the Class of 1953. The forthcoming contest will be the fifth; even in conservative New England it may now be considered as an annual event, if not, indeed, a hardy perennial. But its recurrent flowering is in the hands of the students themselves, on whose continued interest, or the lack of it, its further existence will depend.

As in the last two years, the essay will consist of the report of a clinical case personally studied by the student. As before, the report will be combined with a discussion of the pathologic condition represented by the case and a review of the important literature on the subject, the paper following the usual form of case reports as published in the *Journal*. Thus not only will the participant lay himself, or herself, open to the possibility of winning a substantial prize but will do so in the ordinary course of academic duty.

The other rules of the competition are as follows:

Manuscripts are to be not more than 5000 words in length, clearly typewritten in English, double or triple spaced with references listed at the end in numerical arrangement according to the form used by the *Quarterly Cumulative Index Medicus*. They must be in the hands of the editor by March 15, 1953, and must be accompanied by a certification from the dean of the medical school concerned stating that the author is a member in good standing of the fourth-year class and specifying the expected date of graduation. All manuscripts will become the property of the *Journal*.

A cash prize of $100 will be paid for the best essay of those found to be suitable for consideration; the paper will be published in the *Journal* if the quality is considered to conform to the standards by which the editors usually judge material submitted, and the author will receive a hundred free reprints.

A second prize will consist of a two-year subscription to the *Journal*.

The editors wish to emphasize that in establishing this competition they are interested as much in encouraging good medical writing as in promoting the collection of scientific and clinical material. In judging papers that may be submitted, particular attention will accordingly be paid to clarity, simplicity and general literary excellence.

M. Aran mentions, in the Bulletin de Therapeutique, *that he has succeeded in staying ague fits by the use of the following liniment: Essential oil of turpentine, three ounces and a half; chloroform, about one drachm.*

Boston M. and S. J., *Oct. 20, 1852*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

SMALLPOX VACCINATION AND POLIOMYELITIS

There is no reason to postpone the vaccination of school children against smallpox because poliomyelitis happens to be present in the community. Some parents have been giving this excuse to school authorities, but it should not be accepted as a valid reason for admitting an unvaccinated child.

Work done in the last two years gives some justification for postponing inoculations of whooping-cough vaccine and diphtheria toxoid. There is some association between such inoculations and a slight increase in paralysis in the limb injected, but there is no similar association with smallpox vaccination.

If parents wish to postpone smallpox vaccination, school authorities will require an exemption certificate signed by a physician. This certificate will be good for only two months.

The danger from diphtheria and whooping-cough inoculations is small compared with that of a throat operation when poliomyelitis is prevalent. Those who have the disease within two weeks of a tonsillectomy are likely to have bulbar involvement. It is not claimed that throat operations increase susceptibility; they merely change the variety of the disease if it develops. Nor do diphtheria and whooping cough inoculations make a child more susceptible — they merely slightly increase the degree of paralysis in the injected limb if the disease occurs.

NOTICES

PRIORITIES OF SELECTIVE SERVICE REGISTRANTS

The date on which Priority II special registrants (medical) will be called depends on how long Priority I lasts. It has been estimated that Priority II registrants will be called in March, 1953. However, if 50 or 60 per cent of those in Priority I who are now in a deferred classification are placed in an available classification in the meantime, the date on which Priority II special registrants would be called would be extended for thirty to sixty days.

DIABETES FAIR

The New England Diabetes Association will hold a "Diabetes Fair" on Friday and Saturday, November 14 and 15, from 11 a.m. to 10 p.m. at Horticultural Hall, Boston, in connection with National Diabetes Week. The purpose is to stimulate interest in diabetes and help discover unknown cases of the disease. Dr. Harry Blotner is chairman of the Committee on Public Education and Diabetes Detection. A program of interest to the public, social-service workers, dietitians, medical students and physicians has been arranged. There will be a variety of exhibits. Facilities for urine and blood testing will be available. Free chest x-ray examinations will also be made. On Friday, at 8 p.m., a public meeting on diabetes will be held. The speakers will be Dr. Blotner and Drs. Albert A. Hornor, Frank N. Allan, George Anderson, and Elliott P. Joslin.

SPRINGFIELD ACADEMY OF MEDICINE

A meeting of the Springfield Academy of Medicine will be held on Tuesday, November 11. Dr. William W. L. Glenn, associate professor of surgery at Yale University School of Medicine, will speak on the subject "Cardiac Surgery."

HAMPDEN DISTRICT MEDICAL SOCIETY

The Hampden District Medical Society will hold a joint dinner meeting with the Women's Auxiliary on Thursday, October 30, at 6:30 p.m., at the Hotel Kimball, Springfield. The speaker of the evening will be Dr. Thomas H. Lanman, president of the Massachusetts Medical Society.

SPRINGFIELD HOSPITAL EDUCATIONAL PROGRAM

The educational program of the Springfield Hospital for the month of November is as follows:

November 1
8:30–10:00 a.m. Surgical Service Conference, classroom, second floor.
10–11 a.m. Grand Surgical Rounds, Staff Conference Room.
11 a.m.–12 m. Combined Medical-Surgical Grand Rounds, Staff Conference Room.

November 5
1–2 p.m. Orthopedic Conference, Staff Conference Room.

November 7
11 a.m.–12 m. Grand Medical Rounds, Staff Conference Room.

November 8
8:30–10:00 a.m. Surgical Service Conference, classroom, second floor.
10–11 a.m. Grand Surgical Rounds, Staff Conference Room.
11 a.m.–12 m. Clinicopathological Conference, Staff Conference Room.

November 12
1–2 p.m. Plastic Surgery Conference, Staff Conference Room. Dr. Joseph M. Baker.

November 14
11 a.m.–12 m. Grand Medical Rounds, Staff Conference Room.

November 15
8:30–10:00 a.m. Surgical Service Conference, classroom, second floor.
10–11 a.m. Grand Surgical Rounds, Staff Conference Room.
11 a.m.–12 m. Medical Death Review, Staff Conference Room.

November 18
8:30 p.m. Guest Speaker Conference, Staff Conference Room on the subject "X-Ray Visualization of the Pelvic Viscera" by Dr. Walter W. Williams, geneticist, Springfield Hospital.

November 19
1–2 p.m. Orthopedic Conference, Staff Conference Room.

November 22
8:30–10:00 a.m. Surgical Service Conference, classroom, second floor.
10–11 a.m. Grand Surgical Rounds, Staff Conference Room.
11 a.m.–12 m. Surgical Death Review, Staff Conference Room.

November 26
1–2 p.m. Urological Conference, Staff Conference Room.

November 29
8:30–10:00 a.m. Surgical Service Conference, classroom, second floor.
10–11 a.m. Grand Surgical Rounds, Staff Conference Room.

Every Wednesday from 11 a.m. to 12 noon a psychosomatic and group psychotherapy conference is held in the Staff Conference Room under the direction of Dr. Calvert Stein.

Every Thursday at 3 p.m. a pathological conference is held in the Department of Pathology.

Every Friday from 1 to 2 p.m. a radiological conference is held in the Department of Radiology.

INTERNATIONAL ACADEMY OF PROCTOLOGY AWARD CONTEST

The International Academy of Proctology announces its annual cash prize and certificate of merit award contest for 1952–1953. The best unpublished contribution on proctology or allied subjects will be awarded $100 and a certificate of merit. In addition, certificates will be awarded to physicians whose entries are deemed of unusual merit.

This competition is open to all physicians in all countries, whether or not affiliated with the International Academy of Proctology. The winning contributions will be selected by a board of impartial judges.

The formal award of the first prize and a presentation of other certificates, will be made at the annual convention dinner dance of the Academy in May, 1953.

The Academy reserves the exclusive right to publish all contributions in its official publication, *The American Journal of Proctology and Gastroenterology.*

All entries must be limited to 5000 words, typewritten in English and submitted in five copies. All entries must be received no later than April 1, 1953. Entries should be addressed to the International Academy of Proctology, 43-55 Kissena Boulevard, Flushing 55, New York.

NATIONAL FOUNDATION FOR INFANTILE PARALYSIS POSTDOCTORAL FELLOWSHIPS

The National Foundation for Infantile Paralysis announces the availability of a limited number of additional postdoctoral fellowships to candidates interested in research and teaching in medicine and the related biologic and physical sciences. The fellowships cover a period of from one to five years, with stipends ranging from $3,600 to $7,000 a year and with marital and dependency status being considered in determining individual awards. Institutions that accept fellows receive additional compensation for expenses incurred in their training programs.

Eligibility requirements include United States citizenship (or the declared intention of becoming a citizen), sound health and an M.D., Ph.D. or an equivalent degree.

Complete information concerning qualifications and applications may be obtained from the Division of Professional Education, National Foundation for Infantile Paralysis, 120 Broadway, New York 5, New York.

AMERICAN CANCER SOCIETY CLINICAL FELLOWSHIPS AND TRAINEESHIPS

Clinical fellowships or traineeships of the American Cancer Society will be made available to hospitals offering postgraduate training (residencies and fellowships) in cancer, surgery, specified surgical specialties (obstetrics and gynecology, orthopedic surgery, otolaryngology and urology), radiology, pathology and internal medicine. The institution must be approved for such training by the Council on Education and Hospitals of the American Medical Association, and will be selected on the basis of demonstrated or stated intention of placing emphasis on the diagnosis and treatment of cancer in their training program.

Applicants must be graduates of Class A medical schools in the United States or its territories and Canada, not over forty years of age on the birthday after the beginning of the training and citizens of the United States and must conform in other respects to the requirements of the institution to which he applies. Clinical fellowships will be awarded to physicians who have completed a year of postgraduate training, in addition to internship, for certification by the appropriate medical specialty board in one of the specialties listed in the first paragraph above; applicants for clinical traineeships must have completed a full year's internship. Stipends will be $3600 a year for fellowships and less than that amount (commensurate with the level of training) for traineeships.

Applications from institutions must be filed with the director, Professional Education Section, American Cancer Society, Inc., 47 Beaver Street, New York 4, New York, not later than November 10, 1952. No forms are necessary, but letters of application should include the following information: number of fellowships and traineeships applied for; funds available from other sources for partial support of fellows and trainees; name of person who will supervise the training of the fellow or trainee and to whom he will be directly responsible; date fellowship or traineeship will begin; and a thorough documentation of the training that will be received at the institution, including facilities available (such as tumor clinics and opportunities for diagnosis, treatment and clinical research).

MEDICAL RESEARCH FELLOWSHIPS

The Division of Medical Sciences of the National Research Council announces the following postdoctoral research fellowships for 1953–1954:

There are two groups of fellowships in the medical sciences, one supported by the Rockefeller Foundation, and the other by the Lilly Research Laboratories. Both are administered by the Medical Fellowship Board of the Division of Medical Sciences. These awards are designed to offer advanced training in the preclinical sciences, and not to provide practical experience in the clinical field. Applicants with clinical experience who are seeking fellowships with the object of entering clinical investigation will be expected during the period of appointment to devote themselves to research in the basic medical sciences. The fellowships are intended for recent graduates who, as a rule, are not more than thirty years of age. Fellows must hold the M.D. or Ph.D. degree. The Rockefeller fellowships are open to citizens of the United States and Canada, but the Lilly fellowships are available only to citizens of the United States.

Fellowships in tuberculosis are available under a grant from the National Tuberculosis Association. These awards, which are also administered by the Medical Fellowship Board, are designed to promote the training and development of investigators in fields related to tuberculosis. They are open to citizens of the United States who are graduates of American schools and who, as a rule, are not more than thirty years of age. Preference will be given to applicants who have the M.D. or Ph.D. degree; only in exceptional circumstances will a fellowship be awarded to an applicant without either of these degrees.

Fellowships in radiologic research are administered by the Division for the James Picker Foundation. Applications are reviewed by the Committee on Radiology of the Division. The recommendations of the Committee are transmitted to the Board of Directors of the Foundation for final determination of awards. These fellowships offer research training for recent graduates who, as a rule, are not more than thirty years of age and who are entering upon investigative careers in the field of radiology. The Foundation has expressed particular interest in the support of candidates who propose to carry on research oriented toward diagnostic aspects of radiology. Fellows must hold the M.D. or Ph.D. degree. Appointments are not limited to citizens of the United States.

The Committee on Growth of the Division of Medical Sciences advises the American Cancer Society regarding the award of fellowships in cancer research. Announcement of this program has been published separately.

Applications for 1953–1954, must be postmarked on or before December 10, 1952. Fellowships are awarded in the late winter or early spring. Complete details and application blanks may be obtained from the Fellowship Office, National Research Council, 2101 Constitution Avenue, N. W., Washington 25, D. C.

EXAMINATION FOR PUBLIC HEALTH SERVICE MEDICAL OFFICERS

A competitive examination for appointment of medical officers to the Regular Corps of the United States Public Health Service will be held on January 6, 7 and 8, 1953. Examinations will be held at a number of points throughout the United States, located as centrally as possible in relation to the homes of candidates. Applications must be received *no later than November 25, 1952.*

Application forms and additional information may be obtained from the Chief, Division of Commissioned Officers, Public Health Service, Federal Security Agency, Washington 25, D. C.

(Notices concluded on page xix)